volume 22
number 2
february 1961

MAR 1 6 1961

Diseases *of the* Nervous System

MEDICAL LIBRARY
DES MOINES

Section Two - Supplement

(CONTENTS ON PAGE 3)

MEDICAL LIBRARY
HISTORICAL BUILDING
DES MOINES, IOWA

CARPHENAZINE
(PROKETAZINE*)

Communications Read before Closed
Symposium on Carphenazine

St. Davids, Pa.
September 19 to 20
1960

*Trademark

Printed in U.S.A.

Published by
PHYSICIANS POSTGRADUATE PRESS
277 Broadway - New York 7, New York

Introductory Remarks

Early clinical screening of a phenothiazine compound of the piperazinyl series, 1-[10-(3-[4-(2-hydroxyethyl)-1-piperazinyl]-propylphenothiazine-2-yl]-1-propanone (carphenazine,* or Wy-2445) indicated that this substance was capable of producing a perceptible effect on institutionalized chronic schizophrenic patients whose symptoms had remained static for at least three years or who had shown an insidious and progressive deterioration. Withdrawn, mute patients who had long remained in isolation from their environment under the influence of this agent began to take an interest in themselves and also showed an appreciation of their surroundings. Considering that the spontaneous remission rate in this group is regarded as less than 1 per cent, such preliminary findings encouraged more widespread and definitive investigation.

During the course of two years' study, the compound has been subjected to various researches of conventional design in an attempt to obtain significant data within each individual study, and also to compare the results produced by different investigational procedures.

This symposium** was convoked for the purpose of discussing all aspects of the researches on carphenazine with a view to determining the antipsychotic activity, dosage, flexibility, tolerance, safety and toxicity of the compound; and comparison of similar properties exhibited by other phenothiazine agents of the same class but greater potency.

James A. Page, M.B.B.S.

*Carphenazine is available as Proketazine (Trademark) from Wyeth Laboratories.

**Closed Symposium on Carphenazine, St. Davids, Pa., September 19-20, 1960.

DISEASES *of the* Nervous System

CONTENTS

INTRODUCTORY REMARKS 2
James A. Page

CHEMISTRY OF CARPHENAZINE 5
Peter B. Russell

PHARMACOLOGY AND TOXICITY OF CARPHENAZINE 7
Richard Tislow

EEG EFFECTS OF CARPHENAZINE 14
Michael J. Hosko, Jr.

BEHAVIORAL PROCEDURES USED IN EVALUATION OF THE PSYCHOPHARMACOLOGICAL EFFECTS OF CARPHENAZINE 19
Irving Geller

INHIBITORY EFFECTS OF PHENOTHIAZINE COMPOUNDS ON SELF-STIMULATION OF THE BRAIN 23
Larry Stein

PHYSIOLOGICAL REACTIVITY OF CARPHENAZINE IN PARENTERAL AND ORAL USE 28
Anthony Sainz

IDENTIFICATION, DESCRIPTION AND SELECTION OF THE CHRONIC SCHIZOPHRENIC PATIENT 30
Nolan D. C. Lewis

CARPHENAZINE IN THE TREATMENT OF SCHIZOPHRENIA 37
Jane E. Oltman and Samuel Friedman

USE OF CARPHENAZINE IN SEVERELY ILL PSYCHIATRIC OUT-PATIENTS 42
Sidney Merlis

A COMPARISON BETWEEN TRIFLUOPERAZINE AND CARPHENAZINE IN CHRONICALLY ILL SCHIZOPHRENIC IN-PATIENTS 46
J. Cacioppo, H. Babikian and Sidney Merlis

TREATMENT OF CHRONIC SCHIZOPHRENIA WITH PARENTERAL AND ORAL CARPHENAZINE 51
Douglas Goldman

CARPHENAZINE THERAPY IN HOSPITALIZED PATIENTS 58
Nauttam J. Kothari, In Ho Park, Nathan S. Kline and John C. Saunders

CLINICAL EVALUATION OF CARPHENAZINE 60
D. W. McCreight

FACTORS THAT DETERMINE DRUG-INDUCED AKATHISIA 69
Daniel X. Freedman and Jacob deJong

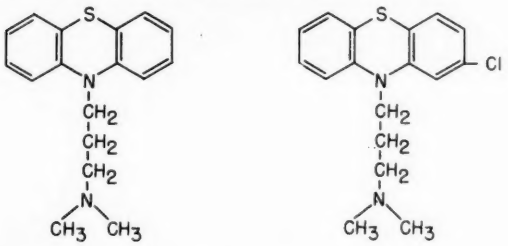
COMPARISON OF THE CLINICAL EFFECTS OF CARPHENAZINE AND FLUPHENAZINE IN CHRONIC SCHIZOPHRENICS 77
Anthony Sainz

SUMMARY OF THE FINDINGS IN PHARMACOLOGICAL AND CLINICAL STUDIES OF CARPHENAZINE 80
Joseph M. Tobin

Chemistry of Carphenazine

PETER B. RUSSELL, PH.D.*

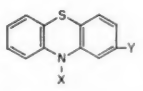
In the beginning, the phenothiazine derivatives were recognized as possessing a multitude of pharmacological activities. It was realized early, however, that certain of these activities could be emphasized or de-emphasized by the introduction of substituents into the nucleus of the phenothiazine compound. An example of this is seen in the comparison of promazine and chlorpromazine (fig. 1). The presence of the chlorine in the latter compound appears to reduce the antihistamine effects and increase certain of the central nervous system effects. It is apparent also that the basic side chain at position 10 has a profound influence on the nature of the pharmacological activity in the phenothiazine series. A comparison of promethazine with promazine serves to illustrate this point.



PROMAZINE **CHLORPROMAZINE**

Figure 1.

It is not essential to give here a detailed account of the effects of structure on activity in the phenothiazine series. Within Wyeth Laboratories alone, some 300 to 400 compounds have been prepared and examined, and undoubtedly a much greater number has been prepared by other workers around the world. Confining our attention only to a small number of compounds that have found their way into the market, we can illustrate some of the principles, however.



NAME	X	Y
PERPHENAZINE	$CH_2CH_2CH_2N$ N CH_2CH_2OH	Cl
PROCHLORPERAZINE	$CH_2CH_2CH_2N$ N CH_3	Cl
TRIFLUOPERAZINE	$CH_2CH_2CH_2N$ N CH_3	CF_3
THIORIDAZINE	CH_2CH_2 N CH_3	SCH_3
METHOPROMAZINE	$CH_2CH_2CH_2N(CH_3)_2$	OCH_3

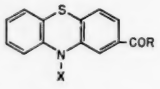
Figure 2.

It is noticed that the phenothiazine derivatives differ from one another in the nature of the basic chain at 10 and in the substituent at 2 (fig. 2). It seems to be generally felt that most profound activity is observed with a negative substituent in one of the aromatic rings of the phenothiazine nucleus. Such a group is one that attracts electrons and is illustrated here by chlorine and trifluoromethyl. It must be said at once that chemically speaking there is a marked difference between these two groups. Both attract electrons. Chlorine, operating by a polar effect, deactivates the whole nucleus but leaves the *ortho* and *para* positions more active than the *meta* position. Trifluoromethyl, on the other hand, deactivates the nucleus but leaves the *meta* position more active than *ortho* and *para* positions. This chemical phenomenon may be connected in some way with the fact that, while a chlorine appears to increase the sedative effects of a phenothiazine compound, the trifluoromethyl, while increasing certain of the central nervous system actions, does not appreciably in-

From the Research Division, Wyeth Laboratories.
*Director, Research Division, Wyeth, Laboratories, Radnor, Pa.

crease the sedative effect. The other substituents, methoxy and methylthio, cannot be looked on unequivocally as negative substituents since they tend to increase *ortho* and *para* activity.

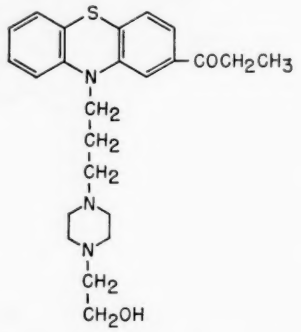
The nature of the side chain also has effect upon the activity of the compounds and it appears that piperazine side chains yield compounds that have lower activity as sedatives but in general have central nervous system effects of a higher level. Obviously then, by juggling these substituents X and Y, phenothiazine compounds with directed specificity may be designed.



Wy	X	R
1172	$CH_2CH_2CH_2N(CH_3)_2$	CH_3
2033	$CH_2CH_2CH_2N$ ◯ NCH_3	CH_3
2422	$CH_2CH_2CH_2N$ ◯ NCH_2CH_2OH	CH_3
2445	$CH_2CH_2CH_2N$ ◯ NCH_2CH_2OH	CH_2CH_3
2475	$CH_2CH_2CH_2N$ ◯ $NCH_2CH_2OCOCH_3$	CH_2CH_3
1321	$CH_2CH_2CH_2N(CH_3)_2$	$CH_2CH_2CH_3$
1377	$CH_2CH_2CH_2N(CH_3)_2$	⬡

Figure 3.

One group of substituents that have negative properties related to trifluoromethyl, rather than chlorine, is the acyl group. In fig. 3 are illustrated some 2-acyl phenothiazine compounds prepared in our laboratory; these are only a few of many selected to illustrate the point. A number of phenothiazine derivatives with the more desirable basic side chains at position 10 were combined with acetyl, propionyl, butyroyl and benzoyl at position 2 of the phenothiazine nucleus; the last two groups appeared to be of little interest. However, the first two groups gave rise to compounds with interesting pharmacological and clinical effects. Two such compounds, Wy 2445 and Wy 2475, appeared to us to possess the useful pharmacological properties required of such an agent. The final choice between these and two or three others rested on the clinical effects of the compounds. Finally, the selection went to Wy 2445, which is carphenazine (fig. 4).



Wy 2445 CARPHENAZINE

Figure 4.

Wy 2445

	DIMALEATE $C_{24}H_{31}O_2N_3 \cdot 2C_4H_8O_4$	DIHYDROCHLORIDE $C_{24}H_{31}O_2N_3 \cdot 2HCl$
m. w.	657.1	498.5
% Base	64.9	85.4
Color	Dull yellow	White
Odor	Odorless	Odorless
Physical Appearance	Fine powder	Crystalline powder
Solubility: H_2O	1%	Easily soluble
95% al.	1%	Easily soluble
Ether	Insoluble	Insoluble
Melting Range, °C	170-172°	232-235°
pH(1% aq. sol.)	3.5	2.9
Potentiometric titration (inflection)	pH 4.85, 8.70	pH 5.0, 10.0

Figure 5.

We have investigated chiefly two salts of carphenazine, the dimaleate and the dihydrochloride. The relevant information regarding these compounds is given in fig. 5. The solubility, both in water and in alcohol, differs rather considerably—the hydrochloride being much more soluble than the dimaleate, which is soluble to the extent of only about 1 per cent in water and in alcohol. The difference in solubility may account for the difference in time of onset of the effects of the drug, which have been reported.

Pharmacology and Toxicity of Carphenazine

RICHARD TISLOW, M.D.

Several series of phenothiazine derivatives prepared in the organic chemistry department of the Wyeth Laboratories were screened in several animal species for various activities. One of these compounds was particularly interesting because of its high activity and low toxicity. Some of the pertinent pharmacological data on this compound, referred to under the name carphenazine (Wy-2445), are presented here.

Table 1 shows the overall behavioral effects in mice produced with increasing intraperitoneal doses of carphenazine, trifluoperazine and chlorpromazine (CPZ), respectively. Catalepsy was marked in carphenazine and trifluoperazine-treated mice and slight in CPZ-treated animals, whereas the degree of sedation was the reverse: slight under treatment with carphenazine, slight to moderate under trifluoperazine and marked under CPZ. Similar behavioral effects were seen in rats.

Table 2 shows the comparative activity of carphenazine and trifluoperazine in protecting mice against the lethal effects of high doses (13.5 mg. base per kilogram, intraperitoneally) of *l*-epinephrine. The figures in the table represent the effective doses in 50 per cent of the animals (ED_{50}), determined from dose-response curves obtained in repeated experiments using at least four dosage levels in 20 animals each. In this test carphenazine was more active than trifluoperazine when the animals were challenged with epinephrine at one, three, five and twenty-four hours after drug treatment.

From the Department of Pharmacology, Research Division, Wyeth Laboratories, Radnor, Pa.

In our interpretation, these results indicate that the inherent adrenergic blocking properties of phenothiazine compounds protect against peripheral and central[1] cardiovascular effects of catecholamines. A central component of action has been assumed by Glassman and co-workers,[2] who have noticed that chlorpromazine, promazine and selenium analogs of promazine exert a long-lasting protective action against epinephrine-induced pulmonary edema. It appears from our data (table 2) that the protective effect against epinephrine death wears off at a relatively rapid rate.

These data in mice are corroborated by pharmacodynamic studies in acute dog blood pressure experiments, which show that carphenazine, upon intravenous injection, is hypotensive, blocks or reverses epinephrine and reduces nor-epinephrine pressor responses. However, these effects are transient and disappear within two hours. Also, tolerance develops to the hypotensive effects upon repeated administration.

Table 3 shows the ED_{50} values of these two compounds in protecting mice against the lethal effect of nicotine.

Nicotine has complex effects on the central nervous system, peripheral ganglia and muscle. At low doses it sensitizes to acetylcholine and renders structures more resistant to it. Nicotine also releases catecholamines from various stores. Thus it is not surprising that several classes of pharmacological substances protect against nicotine, such as anti-Parkinson agents, ganglionic and adrenergic blocking compounds. Presumably the protection afforded by phenothiazine derivatives against nico-

TABLE 1

Behavioral Effects in Mice Seen with Increasing Doses After Intraperitoneal or Oral Administration

Behavioral Effects	Carphenazine	Trifluoperazine	Chlorpromazine
Decreased Motor Activity	marked	marked	marked
Catalepsy*	marked	marked	slight
Jumping	occasionally	occasionally	not seen
Sedation	slight	slight to moderate	marked
Decreased respiration	×	×	×
Clonic convulsions	×	×	×
Death	×	×	×

*Usually more noticeable after i.p. administration.

tine is related to the combined adrenergic and cholinergic blocking effects. The protective doses are higher than those required for epinephrine protection. The antinicotinic effects of carphenazine also appear to be relatively short-lasting.

Table 4 shows the ED_{50} values of carphenazine and trifluoperazine, administered by the subcutaneous or oral route, in antagonizing morphine-induced circling and Straub-tail symptoms in mice. There was not only a quantitative difference between the two compounds—carphenazine being the more active—but also a qualitative difference in that carphenazine antagonized the Straub-tail effect of morphine, whereas trifluoperazine added to this effect. In this connection it should be mentioned that phenothiazine compounds have been screened in morphine-excited cats by Begany and Seifter.[3]

Interpretation of antimorphine effects is complex. It is of interest that three classes of compounds—phenothiazine tranquilizers, meprobamate and sedative-hypnotics, which have obviously different mechanisms of action—are capable of antagonizing morphine-induced circling and Straub-tail symptoms.[4]

Table 5 presents the ED_{50} values of carphenazine and trifluoperazine in protecting grouped mice against the lethal effect of amphetamine.[5] Again, carphenazine was more active than trifluoperazine, particularly in the three hour challenge tests. Carphenazine also gave a slightly higher protection against *d*-amphetamine death in rabbits as compared with trifluoperazine.[6]

This antiamphetamine effect could be of importance because antagonism to the action of amphetamine has been shown by several authors to parallel the tranquilization and deconditioning effects of phenothiazine agents.[7]

TABLE 2

Antagonism to l-Epinephrine in Mice

	ORAL ED_{50} mg. base/kg.			
	1 hr.*	3 hrs.*	5 hrs.*	24 hrs.*
Carphenazine	0.12	0.22	0.34	14.8
Trifluoperazine	0.50	0.58	>1.0	20.0

*Post-treatment Time: Challenge with *l*-epinephrine (13.5 mg. base/kg.) i.p.

TABLE 3

Antagonism to Nicotine Toxicity in Mice

	ORAL ED_{50} mg. base/kg.	
	1 hr.*	3 hrs.*
Carphenazine	7.1	11.5
Trifluoperazine	19.5	19.5

*Post-treatment Time: Challenge with nicotine bitartrate (17.5 mg. base/kg.) i.p.

TABLE 4

Antagonism to Morphine Syndrome in Mice

	ED_{50} MG. BASE/KG.			
	Subcutaneous[1]		Oral[2]	
	vs. Circling	vs. Straub-tail	vs. Circling	vs. Straub-tail
Carphenazine	0.12	0.86	0.24	1.78
Trifluoperazine	0.15	synergism	0.33	synergism

Challenge with 100 mg. base/kg. morphine sulfate i.p.
[1] Challenge ½ hour after drug.
[2] Challenge 1 hour after drug.

TABLE 5

Antagonism to d, l-Amphetamine Toxicity in Grouped Mice

	ORAL ED_{50} mg. base/kg.	
	1 hr.*	3 hrs.*
Carphenazine	2.2	0.27
Trifluoperazine	6.3	4.4

*Post-treatment Time: Challenge with d, *l*-Amphetamine (160 mg./kg.) i.p.

The antiamphetamine effect in mice increased with time. These gradually increasing effects correlated with the behavioral indifference to external stimuli exhibited by cats, dogs and monkeys in other studies in these laboratories, which reached a maximum over a period of three hours. This possibly represents a central action.

Table 6 shows the greater potency of carphenazine in antagonizing Tremorine-elicited tremors in mice. In section A of the table are the ED_{50} values of carphenazine- and trifluoperazine-treated animals challenged with Tremorine at one hour after drug treatment; in section B, those challenged at three hours; in section C, those challenged at five hours; and in section D, those challenged at twenty-four hours. The antagonism to tremors was scored in all four experiments at one-half, one and two hours. In all instances carphenazine was more active than trifluoperazine.

Tremorine antagonism is at present considered the most valid test for anti-Parkinson agents. This test probably represents a measure of central anticholinergic activity. Such activity increased with time, as did the central antiamphetamine effect.

Table 7 shows that carphenazine provided slightly better protection against Metrazol® - induced convulsions and death than did trifluoperazine. At intermediate doses carphenazine had anti-Metrazol effects; however, at higher doses it added to the convulsant potential of Metrazol. This phenomenon is often seen with various other phenothiazine compounds.

Table 8 gives the data on potentiation of narcosis by otherwise nonanesthetic doses of pentobarbital, meprobamate and chloral, respectively. The flatness of the dose-response curve indicates that beyond a certain point, additional dose increments of carphenazine do not result in corresponding increases in potentiation.

The effects of a single subcutaneous administration of 0.15 mg. of carphenazine and perphenazine, respectively, in Rhesus monkeys, are presented in Table 9. The effects on the day of administration were very similar, whereas the post-treatment effects for the following three days were pronounced in the perphenazine-treated monkeys and absent in the carphenazine-treated animals.

We have obtained similar results from a study in dogs under chronic ad-

ministration of carphenazine for one year. Pronounced behavioral effects were seen after each drug administration but had disappeared by the following morning.

Table 10 shows the effects of repeated daily oral administration (eight, nine and ten successive daily doses, respectively) of carphenazine and trifluoperazine in dogs. It can be seen that the effects of both compounds are very similar.

Table 11 shows the acute toxicity of carphenazine by various routes in mice and rats.

After one year on a drug diet of carphenazine, the rate of growth of the rats kept on the lower doses exceeded those of the controls. At the 0.003 per cent dose level in the males, and 0.024 per cent in the females, the rate of growth was similar to that of the control group, whereas at higher dose lev-

TABLE 6

Antagonism to Tremors Produced by Tremorine in Mice

	TIME OF CHALLENGE AFTER DRUG WITH TREMORINE 30 mg./kg. i.p.	ORAL ED_{50} mg. base/kg. OBSERVATION TIME ½ hour	1 hour	2 hours
Carphenazine	1	1.0	0.31	0.17
	3	0.29	0.20	0.08
	5	17.1	7.0	4.0
	24	57.0	25.1	14.0
Trifluoperazine	1	2.30	2.15	0.68
	3	>1.0	>1.0	0.31
	5	43.9	14.8	6.3
	24	>80.0	32.2	20.5

TABLE 7

Effect of Carphenazine and Trifluoperazine on Pentylenetetrazol Convulsions and Deaths in Mice

Phenothiazine Derivative	mg. base/kg. p.o.	PENTYLENETETRAZOL, 1 HOUR AFTER DRUG 60 mg./kg. i.p. Clonic Convulsions	Tonic Convulsions	Deaths	125 mg./kg. i.p. Clonic Convulsions	Tonic Convulsions	Deaths
Carphenazine	0	6/6	2/6	0/6	6/6	6/6	6/6
	1.25	6/6	2/6	0/6	6/6	6/6	6/6
	2.5	5/6	0/6	0/6	6/6	4/6	4/6
	5	4/6	0/6	0/6	6/6	4/6	4/6
	10	4/6	0/6	0/6	6/6	4/6	4/6
	20	4/6	0/6	0/6	6/6	6/6	6/6
	40	2/6	0/6	0/6	6/6	5/6	5/6
	80	5/6	1/6	0/6	6/6	5/6	6/6
Trifluoperazine	0	6/6	2/6	0/6	6/6	6/6	6/6
	1.25	5/6	1/6	0/6	6/6	6/6	6/6
	2.5	4/6	6/6	0/6	6/6	6/6	6/6
	5	5/6	0/6	0/6	6/6	6/6	6/6
	10	6/6	0/6	0/6	6/6	6/6	6/6
	20	5/6	0/6	0/6	6/6	6/6	6/6
	40	6/6	0/6	0/6	6/6	6/6	6/6
	80	5/6	0/6	0/6	6/6	6/6	6/6

TABLE 8

Potentiation of Pentobarbital, Meprobamate and Chloralpentaerythritol Narcosis by Carphenazine in Mice

Carphenazine mg. base/kg. p.o.	DURATION OF TOLERANCE OF SIDE POSITION Average (min.) ± S.E.			
	Pentobarbital*	Meprobamate**	Pentaerythritol	Chloral†
0	4.1 ± 4.1	0.7 ± 0.7	0	
2.5	22.7 ± 7.4	63.3 ± 21.3	51.7 ± 20.7	
5	25.5 ± 6.6	83.3 ± 19.8	66.0 ± 22.2	
10	36.5 ± 4.7	92.9 ± 20.4	71.0 ± 33.3	

*25 mg./kg. i.p.
**200 mg./kg. i.p. 1 hour after carphenazine
†295 mg./kg. i.p.

els there was a decrease in the rate of growth.

At the highest drug concentration, 0.048 per cent, there was a noticeable decrease in the food consumption of both males and females, and also an increase in the spillage, particularly in the females, whereas little spillage was observed in the control group.

A one year study of the chronic toxicity of carphenazine was performed in two groups of 6 dogs each. One group received 5 mg. and one group 10 mg. base per kilogram, in comparison with starch placebo controls. All animals remained in good health throughout the entire study. Continued physical, hematological, behavioral and neurological examinations, as well as terminal liver and kidney function studies, and gross and histological examinations of organs disclosed no pathological changes attributable to drug treatment.

TABLE 9

Effects of Single s.c. Administration of 0.15 mg. base/kg. of Carphenazine and Perphenazine in Rhesus Monkeys (5 in each group)

Behavioral Effects	Score or Per Cent of Animals Carphenazine	Perphenazine
Day of Administration		
Sedation*	3.8	4.0
Catalepsy*	4.0	4.6
Restlessness	80%	100%
Post-Treatment Effects		
24 Hours		
Catalepsy	0%	100%
Sedation	0%	100%
Decreased Appetite	20%	100%
48 Hours		
Catalepsy	0%	60%
Sedation	0%	100%
Decreased Appetite	0%	100%
72 Hours		
Catalepsy	0%	0%
Sedation	0%	66%
Decreased Appetite	0%	66%

*Sedation and catalepsy are graded on a scale of 1-6 at their peak effects and the figures shown represent an average of all animals receiving either compound.

1—possible slight 4—moderate
2—slight 5—moderate to marked
3—slight to moderate 6—marked

Other effects have been tabulated as the per cent of the total number of animals which exhibited the effect.

DISCUSSION

In surveying our data we conclude that carphenazine, among other phenothiazine compounds, has important protective properties against some of the phenomena produced by stress. This may be shown by the ability of these compounds to protect against epinephrine death in single mice and against amphetamine death in grouped mice.

The ability to deal with a stressful situation is probably greatly reduced in the phase preceding the manifestation of mental illness. Some mental disorders might be looked on as the net result of faulty adaptation to stress.

Thus, Selye's concepts of stress and adaptation may be applicable to the development of some mental disturbances.

Society, in dealing with the mentally ill, has found in the past but few solutions—isolation of the individual or sedative-hypnotic medication. However poor, such procedures provided some benefit by reducing stress.

One of the important effects of neuroleptic drugs is a modification in the functional activity of the mesodiencephalic activating system. The resulting attenuation of the sensory input may lower the conscious appreciation of a stressful situation to a level at which it can be adequately handled by a mentally ill person. The virtue of these agents is the accomplishment of such effects without general depression.

With this in mind, it is interesting to speculate as to why the phenothiazine derivatives are more effective in acute schizophrenia than in the chronic phase. In acute schizophrenia, stress is more important than in chronic schizophrenia. This is true because the state of chronic schizophrenia is an adaptation to stress; thus stress becomes less meaningful in chronic schizophrenics. If the phenothiazine compounds act chiefly by protecting the patient from the effects of stress, it would therefore follow that such agents would be most useful in the acute phase of the illness, whereas their therapeutic effectiveness would decrease in the chronic stage.

SUMMARY

Carphenazine possesses an interesting pharmacological profile. It has peripheral antiadrenergic and anticholinergic properties that are relatively short-lasting, as demonstrated by experiments in mice and pharmacodynamic analysis in dogs. The compound has central antiadrenergic effects as exemplified by the antiamphetamine and antimorphine tests in mice, rabbits and cats; and central anticholinergic effects

TABLE 10

Effects of Repeated Daily Administration of Carphenazine and Trifluoperazine at 10 mg. base/kg. p.o. (6 Dogs per Group)[1]

Compound	Sedation[2]	Muscular Weakness[2]	Catalepsy	Tremors	Post-treatment Effects
Carphenazine	1.1	3.0	0.0%[3]	27.8%	Tremors—27.8%
Trifluoperazine	1.2	2.8	27.8%	27.8%	Tremors—27.8%

[1] Study is based on a three-day observation period during the second week of drug administration.

[2] Evaluations of sedation and muscular weakness are based on a scale of 0-5:

0 = no effects
1 = slight
2 = slight to moderate
3 = moderate
4 = moderate to marked
5 = marked

[3] Occasionally cataleptic episodes were seen in this group at other times.

TABLE 11

Acute Toxicity of Carphenazine in Mice and Rats

Species	Route of Administration	LD_{10}	LD_{50}	Limits Lower	Limits Upper	Slope
Mouse	p.o.	119	155.5	142.4	169.8	12.9
	s.c.	51	90.4	77.2	105.1	5.8
	i.p.	55	73.6	66.9	81.1	10.5
	i.v.	30	42.4	38.0	47.3	9.1
Rat	p.o.	73	162.0	85.2	309.0	4.8
	i.p.	68	88.6	76.9	102.1	7.3

as demonstrated by anti-Tremorine tests in mice.

Observations in mice, rabbits, cats, dogs and Rhesus monkeys indicate behavioral effects including slight sedation, reduced motor activity, and relative indifference to environmental stimuli.

Whereas schizophrenia may be caused by a relatively simple metabolic aberration, as suggested by Bleuler, the clinical manifestations of the schizophrenias present very complex pictures, undoubtedly owing to the complexity of the organizational and functional make-up of the central nervous system. The wide spectrum of clinical manifestations may account for the inadequacy of former treatment; e.g., isolation procedures and sedative-hypnotic medication.

Drugs possessing a wide range of activities, such as those provided by some of the phenothiazine derivatives, are required for more successful therapy of schizophrenia, in the absence of a true etiologic treatment.

Acknowledgment: The author gratefully acknowledges the collaboration of S. P. Wilson, M. J. Hosko, D. K. Eckfeld, E. M. Gore, F. V. Hadley, A. J. Begany and H. Pless, all of Wyeth Laboratories, in these studies.

REFERENCES

1. Dasgupta, S. R., and Werner, G.: Inhibition of Hypothalamic Medullary and Reflex Vasomotor Responses by Chlorpromazine. *Brit. J. Pharmacol.,* 9:389-91, 1954.
2. Glassman, J. M., et al.: Effectiveness of Certain Agents Against Pulmonary Edema. Read before the Seattle, Washington, Meeting of the Am. Soc. for Pharmacol. & Exper. Therap., Inc., Aug. 21-25, 1960. *The Pharmacologist,* 2:67, Fall, 1960.
3. Begany, A. J., Seifter, J., Pless, H. H., et al.: Tranquilizing Effect of Phenothiazines in Cats and Rabbits. *Federation Proc.,* 15: 399, 1956.
4. Kouzmanoff, S. P., Eckfeld, D. K., Tislow, R., Seifter, J.: Meprobamate and Phenothiazine Antagonism to Some Morphine-induced Phenomena in the Mouse. *J. Pharmacol. & Exper. Therap.,* 122:40A, 1958.
5. Lasagna, L., and McCann, W. P.: Effect of "Tranquilizing" Drugs on Amphetamine Toxicity in Aggregated Mice. *Science,* 125: 1241-42, 1957.
6. Begany, A. J., and Pless, H. H.: To be published.
7. Bradley, P. B., and Elkes, J.: Effect of Amphetamine and D-Lysergic Acid Diethylamide (LSD_{25}) on the Electrical Activity of the Brain of the Conscious Cat. *J. Physiol.,* 120:13, 1953.

EEG Effects of Carphenazine

MICHAEL J. HOSKO, JR., B.S., M.A.

Before considering the specific electrophysiological activity of carphenazine (Wy-2445), I would like to discuss briefly the technics employed in gathering the data. Three technics were used: acute cat preparations; chronic cat and monkey preparations; evoked potential studies including two different synapses at the motor neuron in the cord, and some exploratory work dealing with the extrapyramidal system.

In the acute cats, surgical procedures were done under ether anesthesia, the skull was exposed, cortical and deep electrode sites were burred open, cortical electrodes were placed visually, and deep electrodes were implanted into specific subcortical areas by means of a stereotaxic instrument. After all manipulation was completed, ether was discontinued, and the animal was immobilized with succinylcholine chloride by constant intravenous drip, and maintained on artificial respiration. After about one to one and one-half hours, the ether had been "blown off" and the animal could be described as an immobilized, unanesthetized preparation.

Chronic cats and monkeys were prepared in essentially the same manner, except that the procedure was carried out under sterile conditions, and the electrode leads were connected to a socket fixed to the skull. The advantages of chronic animals are obvious: they have had sufficient time to recover from any surgical trauma, they need not be restrained, they can serve as their own controls, and comparison of various agents can be done in the same animal over a period of time.

From the Department of Psychopharmacology, Research Division, Wyeth Laboratories.

The changes seen in acute animals were essentially the same as those produced in chronic preparations. Records from only the chronic animals are shown.

Fig. 1 shows the effect of carphenazine at a dose of 0.5 mg. base per kilogram, administered subcutaneously to the monkey. Initial changes were seen in all leads within ten minutes, and were well defined within 30 minutes. Of particular note is the relatively pronounced response in the reticular formation, the posterior hypothalamus and the frontal cortex.

Fig. 2 duplicates the previous record, perhaps more markedly, in another chronic monkey. Again, response was relatively marked in the frontal cortex as well as in the amygdala. The over-all pattern seen in these records resembled that produced by other phenothiazine derivatives, namely, an increase in amplitude, a decrease in frequency, and a high degree of synchrony throughout all leads. These records paralleled the behavioral shift seen in the animals, which went from an alert, highly responsive state to one of sedation and reduced responsiveness.

Fig. 3 illustrates the ability of carphenazine to antagonize amphetamine. The over-all activation pattern of low voltage, high frequency activity is apparent. Activation of the reticular formation was particularly intense. Within 30 minutes after administration of carphenazine, the typical high voltage, low frequency, synchronous pattern dominated the record. The effect on the reticular formation is of particular note.

Fig. 4 shows a block of amphetamine activation in the same cat when car-

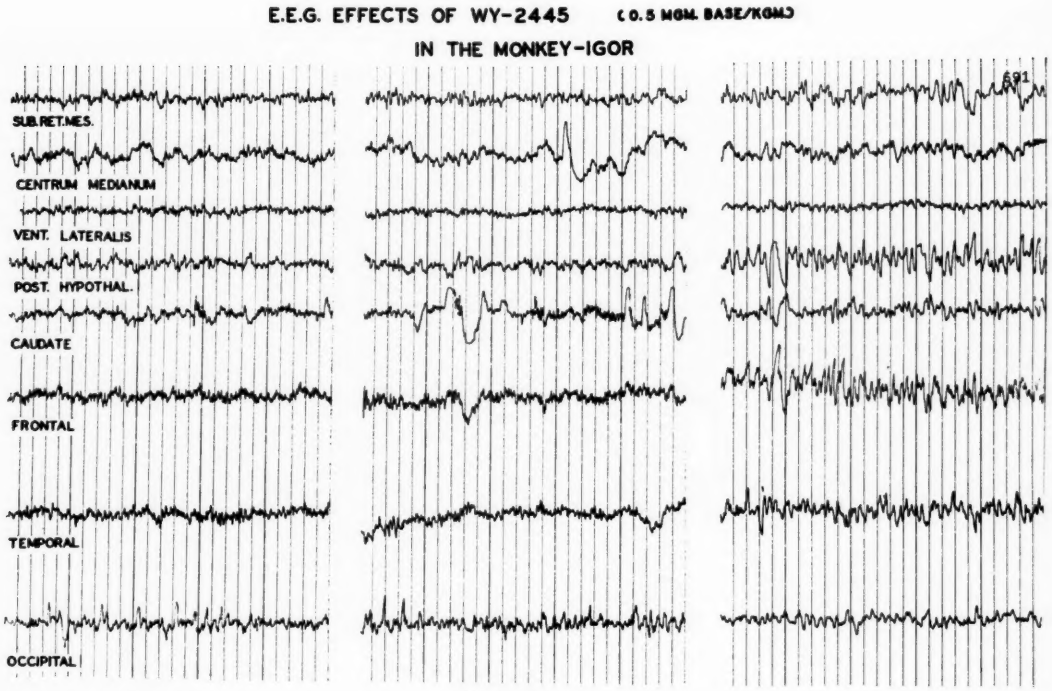


Figure 1.

Control 10 Mins. Post 35 Mins. Post

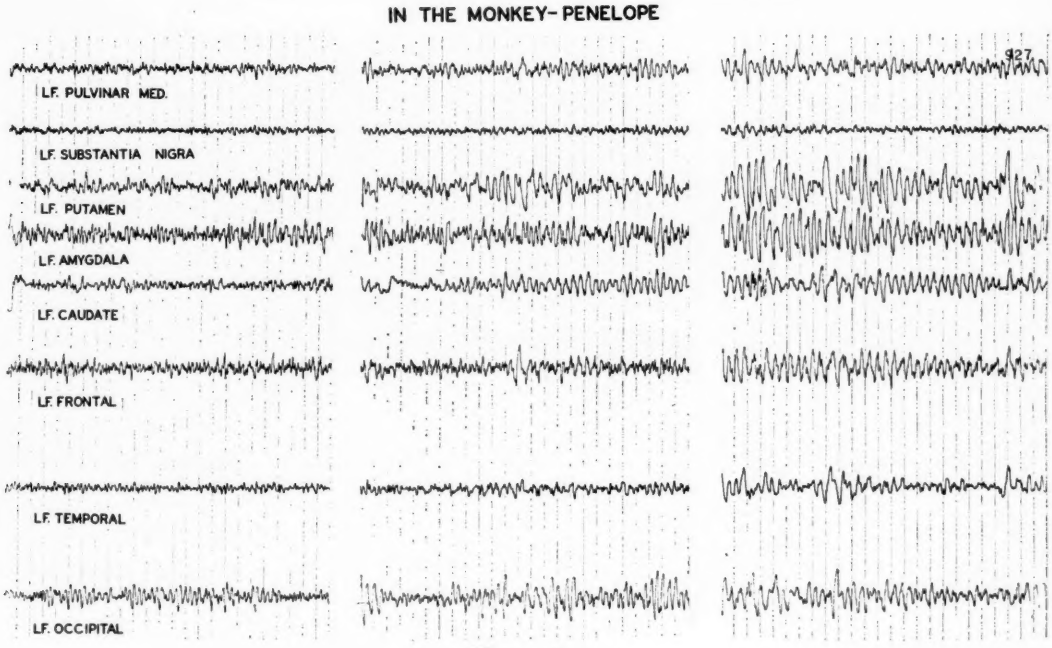


Figure 2.

Control 10 Mins. Post 35 Mins. Post

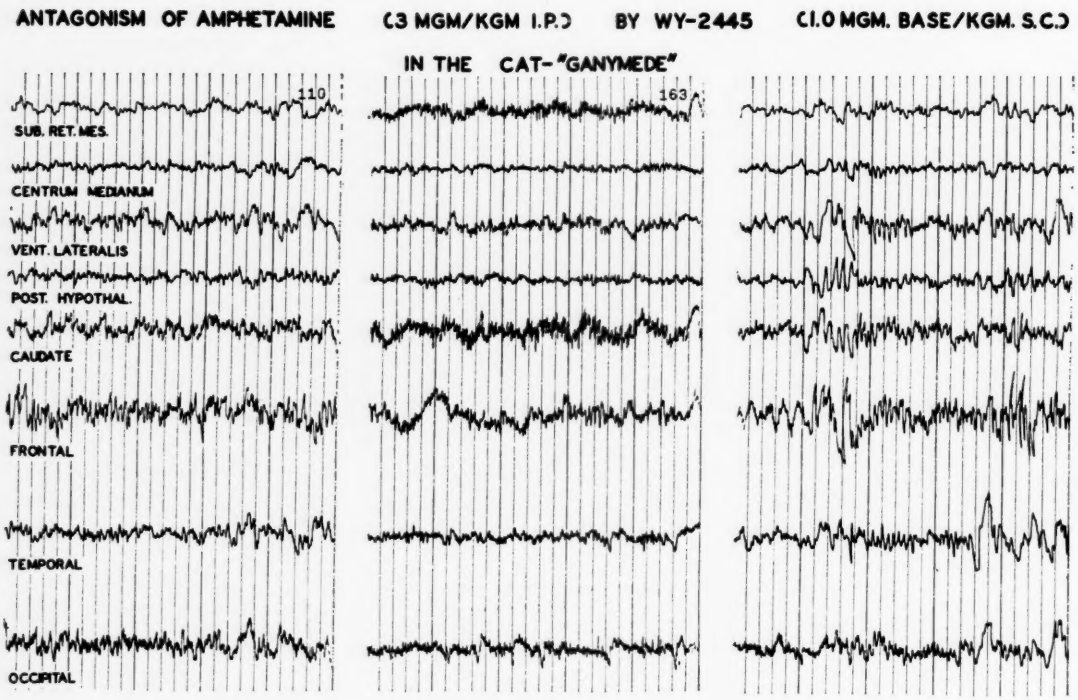


Figure 3.

Control | 30 Mins. Post Amphetamine | 30 Mins. Post WY-2445

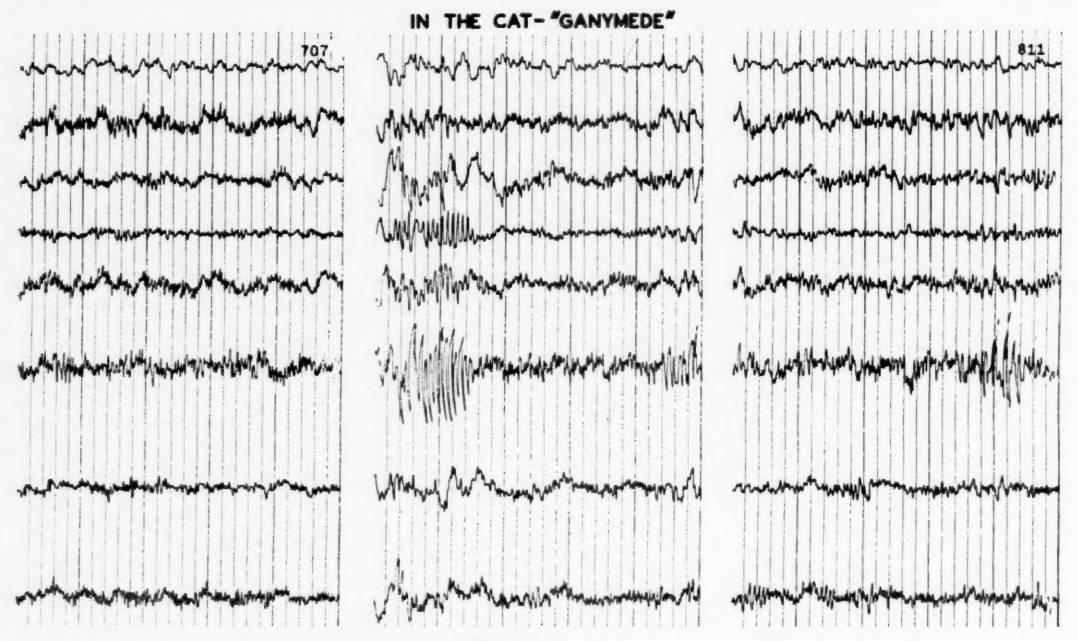


Figure 4.

Control | 20 Mins. Post WY-2445 | 30 Mins. Post Amphetamine

phenazine preceded administration of amphetamine. The lack of activation in the reticular formation is to be noted.

Relatively recent work has provided strong evidence for the existence of both adrenergic and cholinergic components in the ascending reticular system. Bradley has shown that amphetamine produces both EEG and behavioral arousal. Physostigmine, on the other hand, produces EEG arousal without accompanying behavioral effects. It is now becoming apparent that agents affecting the adrenergic component of the reticular activating system produce comparable EEG and behavioral effects; whereas those agents that affect the cholinergic component of the reticular system exhibit a dissociation between the EEG patterns produced and the behavioral response of the animal.

The ability of carphenazine to block the central adrenergic-potentiating effects of amphetamine may be used as a measure of the depression of one component of the ascending activating system by this compound.

Fig. 5 illustrates the difference between the effect of carphenazine and a non-hypnotic dose of pentobarbital at their respective peaks of activity as judged from the EEG. Differences were particularly obvious in the amygdala (4th trace) and caudate (5th trace). The cortical traces of the pentobarbital experiment also tend to run at a higher

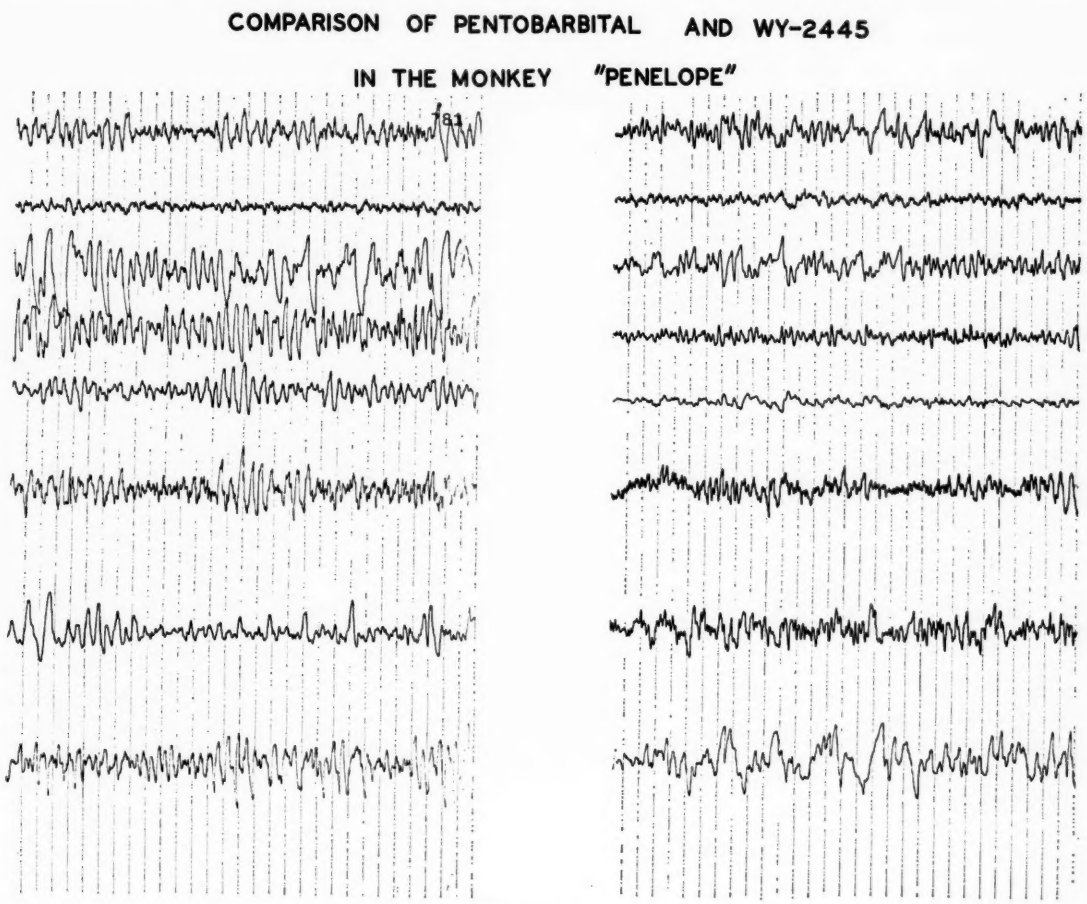


Figure 5.

EFFECTS OF WY-2445
(0.5 MGM. BASE/KGM. S.C.)
ON "AROUSAL MECHANISM"
IN THE MONKEY "PENELOPE"

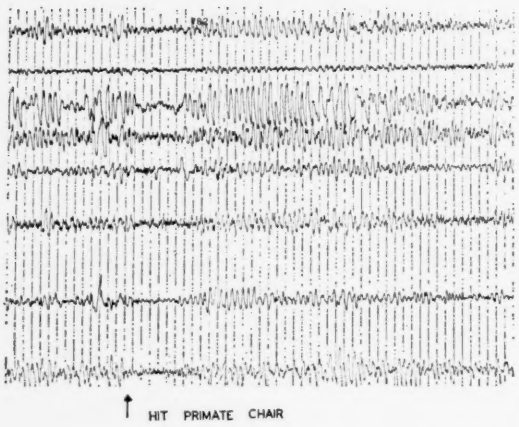


Figure 6.

frequency than those in the carphenazine study.

Fig. 6 shows the almost complete block of a normally powerful arousal stimulus to a monkey in a primate chair. Generally, a single tap on the "chair" will produce an activation pattern lasting many minutes. In this case, it produced a very slight and transient response. This illustrates the ability of carphenazine to block the response of the ascending reticular formation to physiological as well as pharmacological stimuli. Behaviorally, both the cats and monkeys used in these studies seemed to be aware of any activity around them, but their response to all stimuli was greatly attenuated.

Any attempt to study the parkinsonian side effects of phenothiazine compounds in lower animals is doubly difficult, first, because of the functional complexity of the extrapyramidal system, and second, because of the apparent functional dissimilarity between anatomically analogous regions in the lower animals and man. To date, it has not been possible to produce a fully acceptable model of parkinsonism in cats or even in primates.

We have, however, attempted to elicit information on the possible motor side effects of this compound. We have done some preliminary studies using evoked potentials on local and central synapses of the motor neuron in the cord. These studies were essentially negative and consequently imply that the motor effects, if present, are of central origin. As a result of these data, we are now attempting to explore some of the extrapyramidal pathways for alterations which may be correlated with motor impairment.

SUMMARY

1. In the EEG of cats and monkeys, carphenazine produced a pattern of increased voltage, reduced frequency, and high synchrony throughout all the leads studied.

2. Carphenazine is able, in relatively low dosage, both to block and antagonize the central activating effects of amphetamine.

3. Carphenazine produces a marked blocking effect on the ascending reticular activating system.

4. Preliminary experiments indicate that carphenazine has little or no direct spinal effects in the cat.

Acknowledgments: The author gratefully acknowledges the technical assistance of Miss Patricia Townsend and Miss Rosemary Scerni in conducting these studies.

Behavioral Procedures Used in Evaluation of the Psychopharmacological Effects of Carphenazine

IRVING GELLER, PH.D.

The department of psychopharmacology has employed several behavioral procedures in the evaluation of the effects of carphenazine (Wy-2445) as compared with other phenothiazine agents. One of these procedures is termed "discriminated avoidance" behavior. I shall first describe it briefly and then compare the effects of various drugs on the avoidance behavior of a cynomolgous monkey. Fig. 1 illustrates the experimental situation. The monkey is seated in a chair equipped with a lever that can be depressed, an electrifiable seat and foot rest, and a small speaker through which auditory stimuli may be delivered.

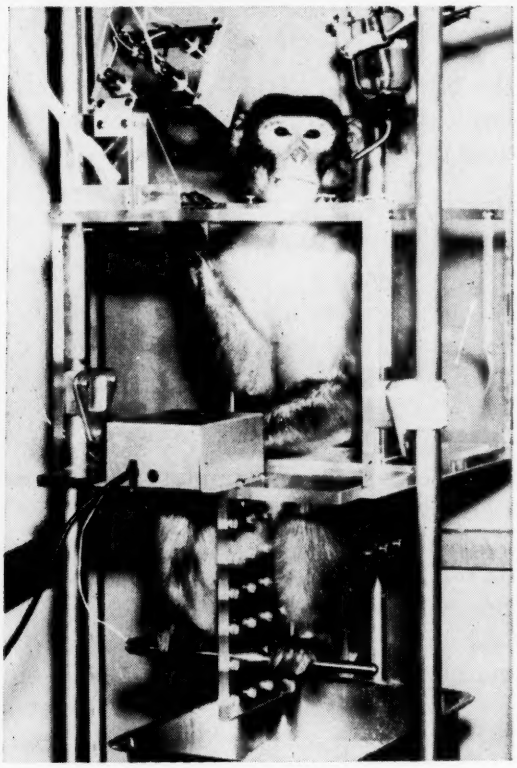


Figure 1.

From the Department of Psychopharmacology, Research Division, Wyeth Laboratories.

Fifteen seconds after the experimental session begins, a five second auditory stimulus (tone) is activated. This tone is terminated contiguously with an electric shock of fixed duration to the animal's seat and feet. The monkey can avoid the shock by responding in the presence of the tone. Such a response (termed the avoidance response) shuts off the tone and delays the onset of the next auditory stimulus for a new fifteen second period. In this way the monkey postpones the next shock by twenty seconds. The effectiveness of a monkey in this situation is measured by determining the ratio of the number of responses in the presence of the tones, or S^D's, to the actual number of tones presented to the animal; i.e.,

$$\frac{\text{Responses in } S^D}{\text{Total No. of } S^D\text{'s}} \times 100 = \% \text{ effectiveness}$$

For example, if a monkey gets 500 tones in a session and makes a lever response in the presence of each tone, his ratio would be 500/500 or an effectiveness of 100 per cent.

The data shown represent a monkey who under control conditions works for a six hour session without taking a single shock, thus performing at 100 per cent effectiveness.

Fig. 2 shows a comparison of the effects of extremely small doses of trifluoperazine, prochlorperazine, and carphenazine upon avoidance behavior. Only trifluoperazine disrupted the avoidance behavior.

Fig. 3 shows the effects of prochlor-

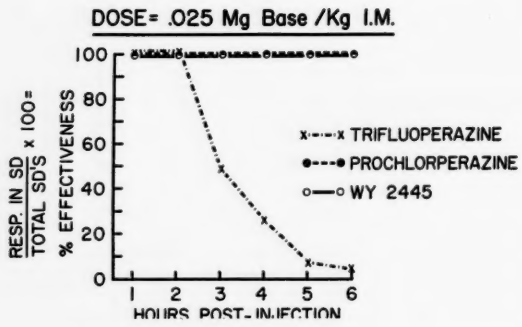


Figure 2.

perazine and carphenazine at twice the dose. As indicated by the first hour postinjection point, the onset of drug action is faster for carphenazine than for prochlorperazine. By the sixth hour the effects of carphenazine have dissipated while prochlorperazine is still active in the monkey.

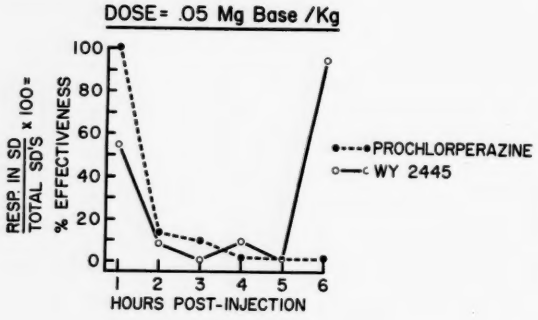


Figure 3.

Fig. 4 shows that a 0.1 mg. per kilogram dose of chlorpromazine is completely ineffective in disrupting discriminated avoidance behavior. The onset of

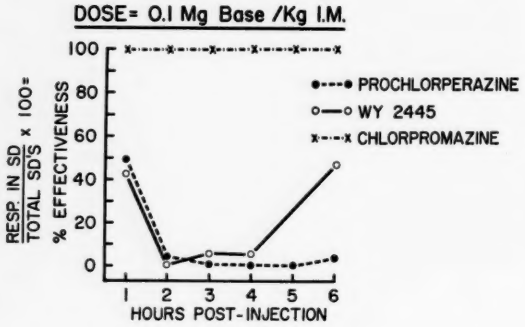


Figure 4.

action for carphenazine is slightly more rapid than that of prochlorperazine. The effects of carphenazine have begun to dissipate during the sixth hour post injection; prochlorperazine is still quite active.

Fig. 5 shows the effects of 0.25 mg. per kilogram doses of carphenazine and trifluoperazine. These compounds appear to be active for roughly the same period of time. On the day following

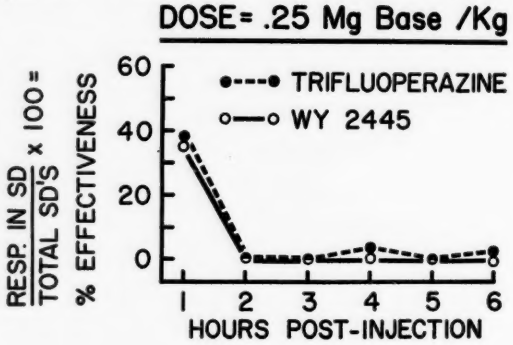


Figure 5.

the injection of carphenazine, the monkey returned to 100 per cent effectiveness in the avoidance situation. On the day after injection of trifluoperazine, however, the avoidance behavior was still disrupted considerably.

In a second approach to the evaluation of these compounds, we employed behavior maintained by positive reward. Thirsty rats learned to press a lever for a water reward, which was obtainable at random intervals on the average of once every two minutes. The rats were given 15 minute lever-pressing sessions once every hour throughout the day. Between lever-pressing sessions the rats were fed laboratory chow pellets in their home cages in order to maintain their thirst. In this way effects of a drug upon the lever-pressing rates could be followed over a ten hour period.

Fig. 6 shows drug effects on the lever-pressing rate of a phenothiazine-sensi-

Inhibitory Effect of Phenothiazines on Water-Rewarded Lever Pressing Behavior

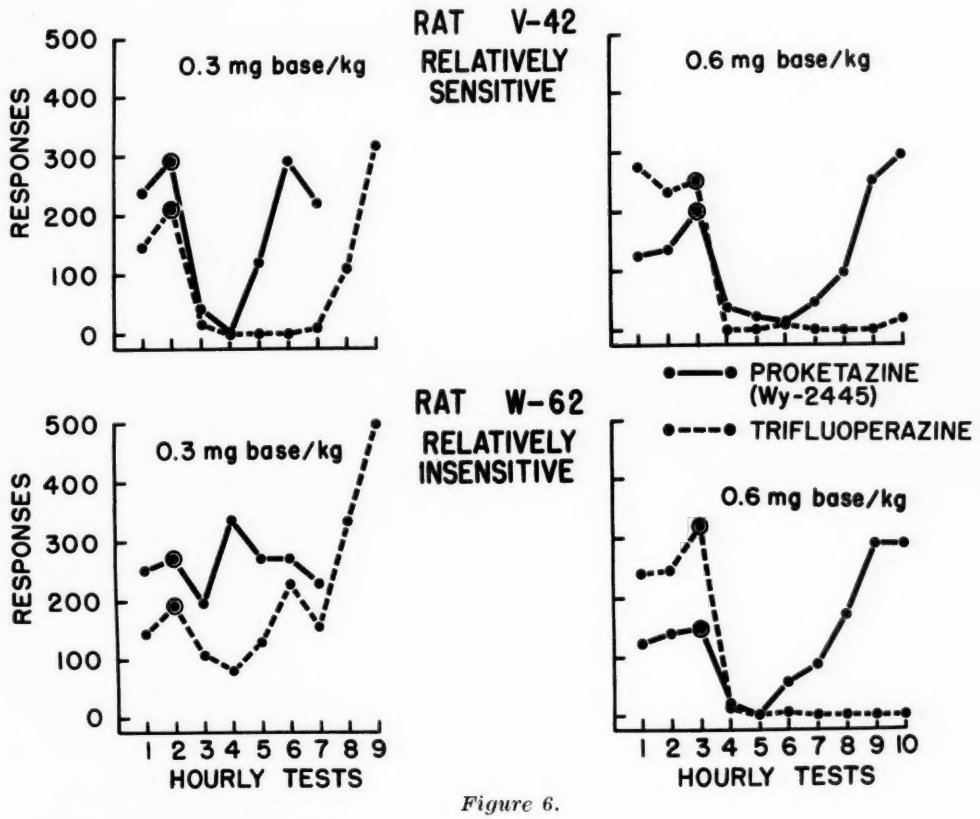


Figure 6.

Inhibitory Effect of Phenothiazines on Water-Rewarded Lever Pressing Behavior

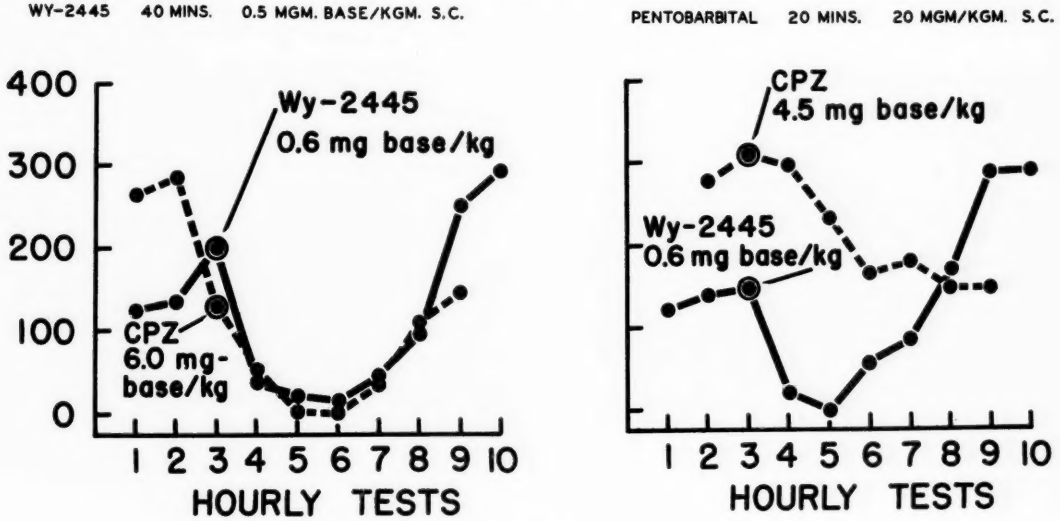


Figure 7.

tive and a phenothiazine-insensitive rat. Each point in the records gives the total response output for each hourly 15 minute test. The circled points indicate the time of injection. Three tenths milligram per kilogram of carphenazine and of trifluoperazine similarly reduced the lever-pressing rates. The effects of carphenazine began to wear off by the third postinjection hour and were completely gone by the fourth hour. The effects of trifluoperazine lasted until the sixth postinjection hour.

After a 0.6 mg. per kilogram dose in the same rat, the initial reduction in lever-pressing rates was similar. The effects of carphenazine began to dissipate on the fourth postinjection hour and were gone by the seventh hour while the trifluoperazine was still active.

In the phenothiazine-insensitive rat, the 0.3 mg. dose had no effect in reducing the lever-pressing rate. The 0.6 mg. dose of carphenazine and of trifluoperazine had approximately the same effect initially. The effect of carphenazine was dissipated rapidly; that of trifluoperazine was lasting.

Fig. 7 compares the effects of chlorpromazine and carphenazine on the response rate of the same two rats. In the phenothiazine-insensitive rat, chlorpromazine at approximately seven times the dose of carphenazine did not reduce lever-pressing to as great a degree as did carphenazine. Ten times as much chlorpromazine was needed to produce the same effect as of carphenazine upon the lever-pressing rate of the phenothiazine-sensitive animal.

From these experiments, we may conclude that carphenazine is similar to other phenothiazines in that it tends to wipe out learned behavior, regardless of whether the behavior is positively or negatively reinforced. This compound is much more potent than chlorpromazine, is more rapid in onset of action than prochlorperazine, and falls into the same potency class as trifluoperazine and prochlorperazine but has shorter duration of action.

Inhibitory Effects of Phenothiazine Compounds on Self-Stimulation of the Brain

LARRY STEIN, PH.D.

Tranquilizers of the phenothiazine type are especially effective against manic psychoses or psychotic agitation. Such disturbances may be viewed as behavior that is out of control. The physiological psychologist James Olds[1] agrees in principle with the Freudian view, which proposes that such psychotic agitation is caused by pathological hyperactivity of reward or pleasure mechanisms. Thus, the behavior is runaway because the reward mechanisms that motivate the behavior are runaway. This suggests that at least part of the action of the phenothiazine derivatives in calming agitation is to inhibit, and hence restore balance to, the reward mechanisms of the brain. If this is true, then new phenothiazine compounds should be examined for their activity against the reward centers.

Olds[2] and others have shown that the reward system is located in a series of subcortical structures that center on the hypothalamus and run the length of the brain from the cingulate cortex and septal region to the reticular formation of the midbrain. The activity of these structures is best studied by means of self-stimulation experiments, in which unanesthetized, freely moving animals may be used.

Electrodes are permanently implanted in the hypothalamus and other reward sites, as in fig. 1, which shows a freshly operated rat with two electrodes. Each electrode consists of a pair of fine platinum wires, twisted together and insulated except at the tips. When the animal is ready for the self-stimulation tests, he is connected to the electrical stimulator by plugging in the connector shown to the right. The metal jacket screws down over the threaded nylon electrode to hold the connection secure throughout the experimental session.

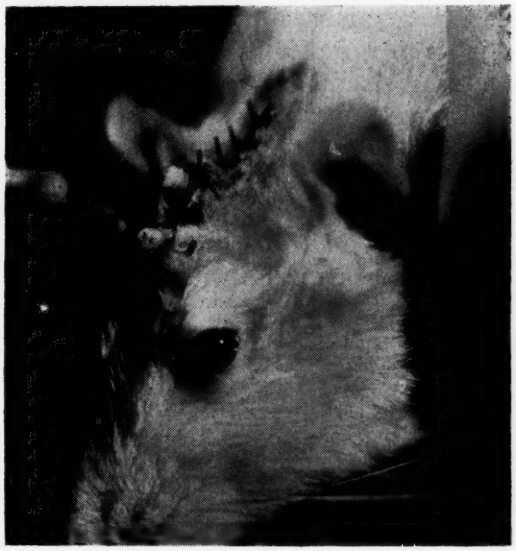


Figure 1.

In the self-stimulation experiment the animal is trained to perform a response, like pressing a lever, to obtain a brief train of rewarding electrical stimulation. When the electrode is located in a highly rewarding brain site, such training may take no longer than a couple of minutes. In certain brain sites, the rewarding effect is phenomenal; animals will work without pausing at rates of up to 8000 self-stimulations per hour, to the point of physical exhaustion. Surely, here is an example of runaway behavior.

We have refined the self-stimulation technic to get information about self-

*From the Department of Psychopharmacology, Research Division, Wyeth Laboratories.

stimulation thresholds.[3] In our technic the animal tells us, through his response pattern, what are the smallest electrical currents that still will satisfy him.

The procedure is illustrated in fig. 2. The animal works in a two lever chamber as illustrated. To obtain the rewarding electrical stimulation, the animal must operate the lever marked "Stim." Each successive brain shock, however, is reduced in intensity by a small step. We obtain our best results with 15 to 20 equal current steps between a moderately rewarding top value and zero. The second lever can be operated at any time to reset the current to the top step. The reset lever never gives brain shocks. In this procedure, then, the animal operates the stimulation lever until the current is driven down to a nonrewarding or unsatisfactory level, and then tells the experimenter what this level is by operating the reset lever.

The projected detail in fig. 2 diagrams this sequence of events. The short horizontal bars on the ordinate indicate the 17 current steps that are available. The recording pen, following the decreasing brain shocks, starts at the top and moves downward one step with each response at the stimulation lever. When the current is driven below the reward threshold, the reset lever is activated, resetting the stimulator and the recording pen to the top. The animal then starts the next stimulation series. The jagged edge of the curve at the bottom gives, in sequence, the current intensities at which resets occurred, and thus traces the reward threshold.

An actual record of performance for a highly trained animal appears in the upper section of fig. 2. The stability of

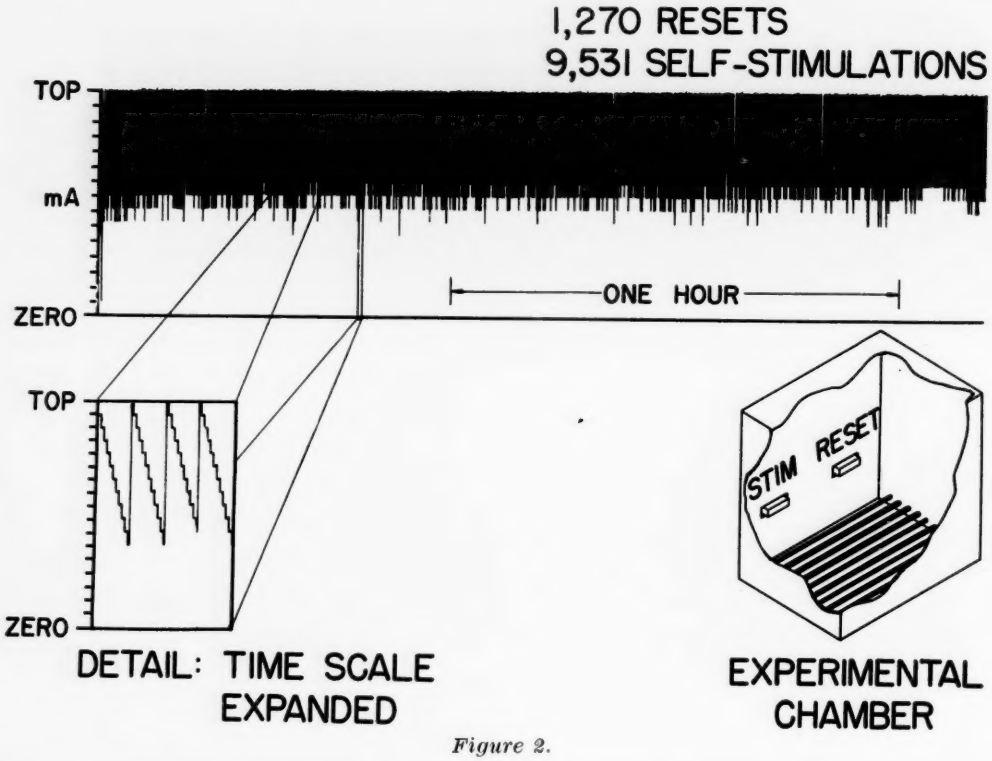


Figure 2.

the performance is evident. With three or four days' rest between experiments, records like this one can be obtained for months, thus permitting the comparison of many different drugs within the same animal.

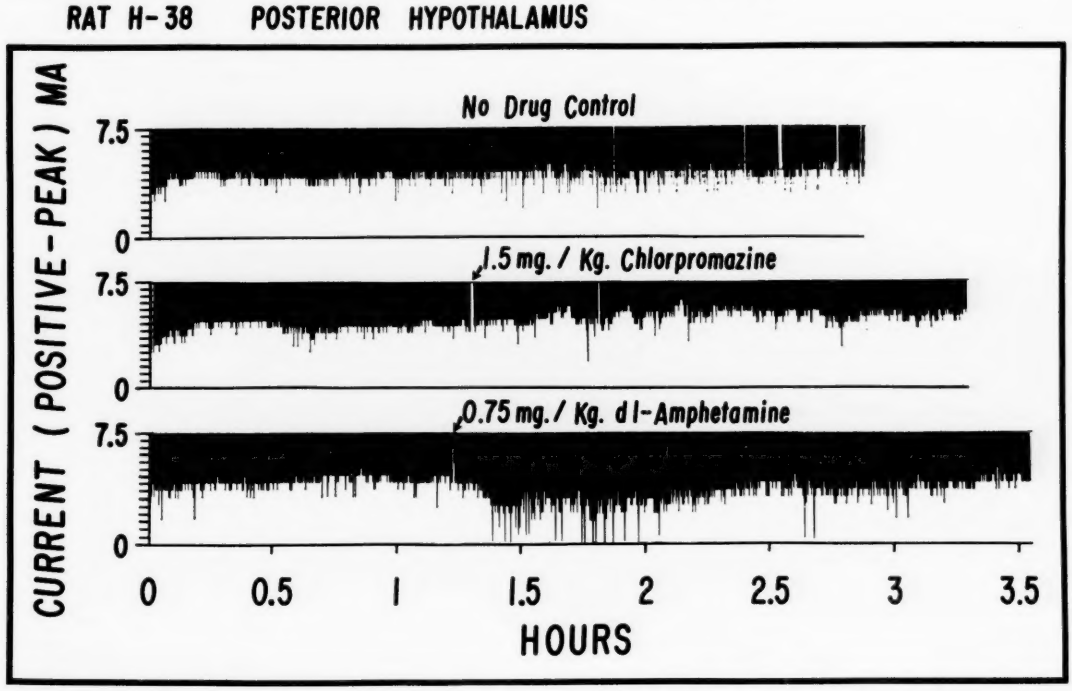


Fig. 3. Sample drug actions mapped through changes in the "threshold" for brain-stimulation reinforcement in the rat posterior hypothalamus. Each record shows the course of reset intensities for an entire daily session. The ordinal markings indicate the 16 current levels available. (After Stein and Ray.[3])

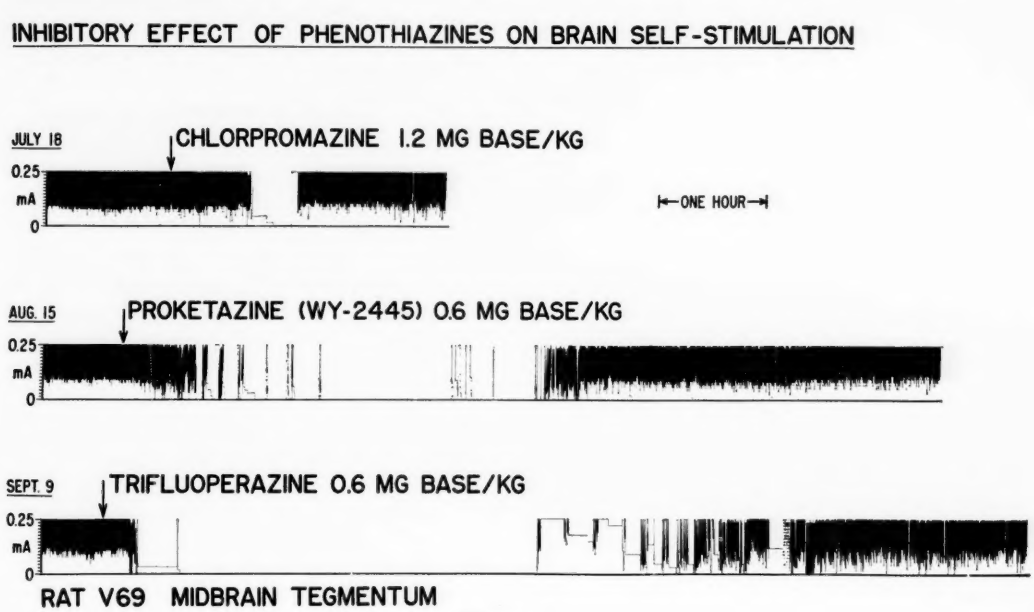


Figure 4.

Most animals with good rewarding electrodes work enthusiastically in this situation; in the two hour period shown here, the animal gave himself over 9500 brain shocks and reset the current more than 1200 times. With response rates at this level, the reward threshold is effectively sampled once every six seconds.

Fig. 3 contrasts the actions of chlorpromazine, a central depressant, and amphetamine, a central stimulant, in an animal with an electrode in the posterior hypothalamus. Each record represents an entire daily session, spaced a week apart. The dose of chlorpromazine chosen was small (1.5 mg. per kilogram of the total salt, or about 1.35 mg. base per kilogram), and shows how this drug elevates the reward threshold without disrupting the performance. About 15 minutes after the chlorpromazine injection, resetting occurred at higher current steps. In contrast, *dl*-amphetamine lowered or sensitized the reward threshold; resetting occurred at lower current steps in a nicely graded fashion, starting five minutes after the injection. The baseline was partially recovered in the case of both drugs, but the sessions were terminated prior to complete recovery.

Fig. 4 compares the inhibiting effects of chlorpromazine, carphenazine and trifluoperazine on the self-stimulation performance of an animal with an electrode in the midbrain reticular formation. Both carphenazine and trifluoperazine were much more potent than chlorpromazine. Although twice the dose of chlorpromazine was used, the inhibitory effect on self-stimulation lasted only a fraction of the duration of the effects of the other drugs. Trifluoperazine had a clearly longer duration of action than carphenazine.

One important aspect of these inhibitory effects should be made clear. The motor activity of the animals appeared in no way impaired, and no obvious effects of the drug were discernible by casual observation. It just seemed that the animals were no longer interested in brain stimulation.

This is the same picture that Dr. Geller showed with monkey avoidance and rats lever-pressing for water. The correspondence among these three sets of

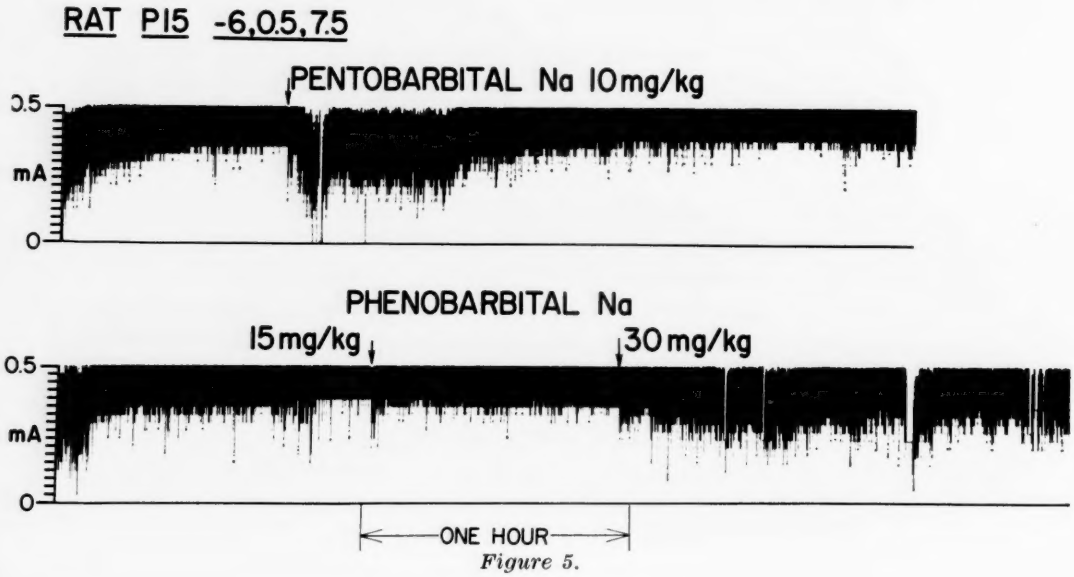


Figure 5.

data seems impressive, since the testing situations varied with respect to the underlying motivation (shocks, water reinforcements, and electrical brain stimulation) and since two species, rats and monkeys, were used.

Fig. 5 shows that the inhibitory action of the phenothiazine compounds in this situation may be clearly differentiated from the action of the barbiturates. Here, potentiating or sensitizing actions of subhypnotic doses of both pentobarbital and phenobarbital are seen. Pentobarbital is more potent than phenobarbital (10 vs. 30 mg. per kilogram), but phenobarbital is longer-acting. Self-stimulation can be inhibited by the barbiturates but only at dosages that eliminate motor activity.

In contrast, self-stimulation is eliminated by the phenothiazine derivatives at doses so small that no apparent effect is observed on the animal's behavior, except that, as mentioned previously, it no longer seems to be interested in brain stimulation. The same, of course, is true of the effect of these agents on psychotic manic states.

Acknowledgments: Thanks are due to Dr. J. Seifter for helpful suggestions, and to Karey Sledge for technical assistance.

REFERENCES

1. Olds, J., and Travis, R. P.: Effects of Chlorpromazine, Meprobamate, Pentobarbital and Morphine on Self-Stimulation. *J. Pharmacol. & Exper. Therap.,* 128: 397-404, 1960.
2. Olds, J.: A Preliminary Mapping of Electrical Reinforcing Effects in the Rat Brain. *J. Comp. & Physiol. Psychol.,* 49: 281-285, 1956.
3. Stein, L., and Ray, O. S.: Brain Stimulation Reward "Thresholds" Self-Determined in Rat. *Psychopharmacologia,* 1: 251-256, 1960.

Physiological Reactivity of Carphenazine in Parenteral and Oral Use

ANTHONY SAINZ, M.D.*

This study of carphenazine was started early in 1959. The physiologic effect of the compound was determined in a special study comprising 43 patients, 20 females and 23 males, ranging in age from 23 to 48 years. All corresponded to the classification of chronic schizophrenia as defined in "Rapid Screening of Phrenopraxic Drugs,"[1] and all were physically healthy except for two who had epilepsy, one who had arteriosclerosis with moderate hypertension, and one who had Grade III nephrosclerotic hypertensive disease.

All of these patients received placebos for one month during which time basal physical, laboratory and psychiatric studies and ratings were performed. Instrumental exploration and laboratory examinations included: electroencephalograms, electrocardiograms, phonocardiograms, digital plethysmograms, dynamic blood pressure studies, complete blood counts, and urinalyses; fasting blood sugar, serum cholesterol and nonprotein nitrogen determinations, alkaline phosphatase, serum transaminase and phenothiazine excretion tests were done; blood catecholamine determinations in conjunction with the plethysmogram also were made.

On determination of the basal ranges, electroencephalograms, electrocardiograms and blood pressure dynamic studies were performed after intramuscular administration of carphenazine in graded doses of from 20 to 80 mg. The maximum dose was reached by addition of 20 mg. increments on different days. For example, on Monday the patients would receive 20 mg. The next trial would be held on a Wednesday, at which time they would receive 40 mg. At the next trial, on a Friday, 60 mg. would be administered, and so forth.

These special studies in human pharmacology were conducted for a minimum of six to a maximum of nine months. During this period all patients in the group received a daily dose of no less than 150 mg. carphenazine orally. Six patients were maintained for nine months on 400 mg. four times a day, by mouth, for a total daily dose of 1.6 Gm.

During treatment blood counts were done on an average of twice a week; urinalysis, three times a week. Blood chemistry determinations were performed one week after each change of dose.

The daily dose in each case started at 100 mg. administered in divided doses of 25 mg. each and ranged to 1.6 Gm., administered in divided doses of 400 mg.

The electroencephalographic patterns were not modified by carphenazine, except for indications of drowsiness in 20 per cent of the patients at the four highest doses. In this there was fairly good correlation with the animal data. With intramuscular doses of up to 80 mg. there was no increased potentiation of amplitude on the EEG, as observed with the preliminary doses, nor were increased abnormalities detected on increase in observation time. The decrease in frequency, at the doses used, averaged not more than 10 per cent in

From The Marcy State Hospital, Marcy, N.Y.
*Director of Research, Marcy State Hospital, Marcy, N. Y.

any case, and increase in amplitude was not more than double the basal amplitude. The changes appeared in approximately ten minutes after intramuscular injection.

Abnormal electroencephalographic patterns were neither provoked nor facilitated in the epileptics, and we were unable to produce seizures even when these patients were relatively free of their basic antiepileptic medication. Most of them had been receiving Dilantin® or Benzedrine® with Dilantin. The anticonvulsant medication was discontinued for about three days and the tests repeated; no seizures developed.

Plethysmographic responses showed transition to normal patterns in 68 per cent of patients for whom the tracing previously had indicated constriction or abnormal startle reactions. There were no significant changes in the individuals for whom the plethysmographic tracing had not been abnormal before.

Artificial abnormalities produced by administration of catecholamine were not normalized, leading to the belief that in humans carphenazine has little, if any, anticatecholamine effect, and possibly lacks angiolytic properties. We were not able to eliminate true neurotic anxiety with carphenazine in three neurotic patients, although we were able to do so with other agents. As a matter of fact, in many of these patients anxiety was increased by medication with carphenazine, an observation to be described in the clinical paper.

Electrocardiographic changes did not occur, even when postural hypotension supervened. Dynamic blood pressure studies indicated that carphenazine dimaleate administered intramuscularly might produce postural hypotension in about 10 per cent of cases, but only at doses of more than 40 mg. Even at this level few experienced hypotension.

The average reduction in blood pressure ranged from 2 to 15 mm. of mercury. The mechanism consisted of dilation of the capillary bed.

Red and white blood cell counts did not vary significantly in this study. It is remarkable that the usual phenothiazine pattern of initial leukocytosis, lowered monocyte count and eosinophilia was observed in only 3 per cent of the group. Special spot tests indicated that competitive inhibition of riboflavin was absent; this finding, together with the blood picture, leads us to believe that blood dyscrasias need not be feared from this compound. No abnormalities in quality or quantity were encountered in the other laboratory determinations performed. Findings in kidney function tests carried out in the nephrotic patient disclosed no alteration.

Phenothiazine excretion tests after ingestion of the compound showed that carphenazine dimaleate appears in the urine in about an hour and a quarter.

The somnolence and the tendency to hypotension were inclined to subside with time. The so-called extrapyramidal reactions tended, on the contrary, to appear only after prolonged administration of the compound, in most cases. However, some sort of central nervous system reaction developed in some patients within a few days of the start of treatment. The significance of this has not been fully determined, but the data lead us to assume that electroencephalographic abnormalities already existed in all such patients; therefore, they reacted more promptly.

A review of our results shows that carphenazine possesses the lowest toxic index of all the phenothiazine compounds we have studied so far.

REFERENCES

1. Sainz, A., et al.: Rapid Screening of Phrenopraxic Drugs. *Psychiat. Quart.*, 32:273-80. 1958.

Identification, Description and Selection of the Chronic Schizophrenic Patient

NOLAN D. C. LEWIS, M.D.

Psychiatry is the description and analysis of mental disorders that require months and years for evolution. Therefore, in a sense, all or most of them are chronic, the question being how much is rigid and irreversible in these syndromes, and how much is reversible and can be changed. Careful records of conscientious and methodical observation are required; precision must replace impressionistic methods. We need less discussion of generalities and more records of well observed cases, especially records covering the entire lifetime, not merely snatches, picturesque symptoms or interpretations in traditional terms. Not every paper should contain complete case histories, but it is necessary to know something about the historical development of the cases before initiation of treatment.

Schizophrenia may be defined as an illness of which the etiology has ranged in theory from the heredoconstitutional-organic to the primary psychogenic. In schizophrenia there is a progressive disarticulation of the individual from his environment; and also disorganization, within the individual, between mental structure and function, with eventual breakdown of mental ability. The rate of progression is something of a measure of the speed and seriousness of the process.

In the old days, Kraepelin approached this subject by thinking in terms of organic disease. He tried to determine the etiology and to discover a basic pathology, but failed. He did, however, establish the usual course and outcome. He pointed out that schizophrenic patients tend finally to reach such a stage of deterioration that they live practically a "vegetable" life. He emphasized, however, that some patients do recover. The old classical categories as he differentiated them are well known.

There is at present no universally accepted theory for the etiology of schizophrenia. There is much disagreement and argument over concept and terminology. Some investigators favor an organic morphologic basis, and others want to explain it in terms of function, utilizing the concept of homeostasis. The vast majority find it most satisfying and soothing to explain schizophrenia in terms of the Freudian unconscious processes. Some others insist that schizophrenia is not really a mental disorder; that the schizophrenic is just a person with a few twisted habits produced by an unresolved Oedipus complex—that the schizophrenic make-up represents a special type of personality.

Others consider schizophrenia a group of serious mental disorders that should be differentiated, separated, and possibly treated differently. Still others regard schizophrenia as a deep-seated unitary disease that may be expressed in several different ways, analogous to typhoid fever, for example. Fifty years ago typhoid fever appeared in so many different clinical guises that it was frequently difficult to reach a correct diagnosis, despite the presence of the bacillus, demonstrable in the center of the picture. Another analogy is that of

From the Bureau of Research in Neuropsychiatry, Princeton, N. J.

syphilis, a paradigm of diseases which mimicked so many others that Osler said, with tongue in cheek, that everybody has syphilis. This evoked tremendous criticism in the newspapers, who did not know Osler's dry humor and did not understand that all he was saying was, "Don't neglect to look for and rule out syphilis."

In so-called chronic schizophrenia, the length of hospitalization varies considerably. In some cases the patients are "in and outers." These must differ physiologically in some way from those whose disorder runs an even, unremitting course. There are also other cases in which the patients have been ill for a long time, and probably had been heavily predisposed before the actual breakdown. An example is one young woman patient of mine who had failed in a beauty contest and who subsequently blew up into an acute turmoil type of schizophrenia. The acute episode subsided to a chronic stage, in which she remained for years. Probably she is still in a hospital. Such a situation, although apparently simple on the surface, may have a deep significance. This patient must have been making a very marginal adjustment for a long time, to have been precipitated by such a minor exciting factor into a lifelong schizophrenia.

What are some of the chronic characteristics emphasized by psychiatrists? Some patients may exhibit annoyance at being questioned or forced to mental exertion; their attention is difficult to obtain and hold. Answers to questions during examination are hit or miss; the patient may not notice self-contradictions, or may say, "I don't know," or something similar, to gain relief as soon as possible from the examining procedure. Seclusiveness, reduction of interest in the environment or hallucinations may occur; many chronic schizophrenics experience delusions. Systematized delusions, however, certainly play a very small part. In a schizophrenic who has been quiet for years, tension may develop into an episodic outburst. There is a dilapidation of thought and judgment, and often negativism, persistent postural oddities, symbolic attitudinizing, or malignant tics. Hypochondriasis in such cases is usually dominant and bizarre; mental oddities progress by increase in shifts, finally with regression to the vegetative level. Most chronic schizophrenics show one or more of what Dr. Kline likes to call "clusters" of signs and symptoms. There are different kinds of clusters, and I think clusters of biological events mean quite a lot.

A good many years ago Bleuler indicated that there is not only a splitting of the psyche in schizophrenia but also a splitting of the physiology into irregularities. In reviewing the work done on the biochemistry of schizophrenia over the last 50 years, one will find many oddities in metabolism that are not consistent for the group. Curious blood sugar and metabolic curves may be observed, of which individual ones may be different, but if one were to study a lot of them they would cancel each other out.

I don't believe schizophrenia is a multiplicity of diseases, but a unitary disorder in which the differences in presenting symptoms are determined by the differences in the personality and experiences of the individual. My reason for such belief, and I would defend it by debate, is that the mechanism of schizophrenia, as we know it and as we describe it, is the same all over the world. A psychiatrist can diagnose schizophrenia in any country, even in remote areas. The content of the hallu-

cinations may be different, according to the culture; however a good many therapists don't differentiate between mechanism and content.

In the most primitive societies one can diagnose three disorders: schizophrenia, epilepsy and feeble-mindedness. One can debate whether manic-depressive psychoses or neuroses are present in primitive societies, but schizophrenia is found and recognized wherever a psychatrist has been able to make observations.

The universality of schizophrenia gives it the earmarks of a disease that certainly has deep-seated somatic components. I dislike to make the distinction that "this is biologic," "this is psychologic," and "this is sociologic." I was trained that biology includes everything that lives. If one wishes to make a distinction, which one should, the terms "somatobiology," "sociobiology" and "psychobiology" are definitive.

A lot of speculation and a lot of imagination have been included in the studies of schizophrenia. When I am accused by doctors other than psychiatrists of being too imaginative, I point to the radiologists. They sometimes see indications of lesions that are not found at autopsy. Having performed autopsies for ten years, I speak from experience on this point. The psychiatrist, like the radiologist, may sometimes see something that is important but not clearly defined.

Bleuler emphasized at least five symptoms as fundamental characteristics of schizophrenia. One was that logically unrelated ideas are related in the patient's mind. You can find this phenomenon even in unrecognized schizophrenics: patients who are not sick enough to be hospitalized.

Another sign is the combination of ideas, by a condensation process, often into an odd statement in symbolic speech. An example is the ward patient whom I had to tell that his favorite brother had just died. It was an unwelcome duty because he was making a fair adjustment. When I told him, having first prepared him a little by telling him how loved ones die, he spoke up and said, "Men and dogs, dogs and men, bad dogs, good dogs, good and bad men." What was he saying? That this is a law of life: all animals and all men die, whether they are good or bad. You must recognize that kind of condensation to understand the schizophrenic.

The next symptom is expressed in general vague notions rather than in the concrete statements of the normal individual. The schizophrenic has a "labyrinthine" mind, that goes 'round and 'round.

Another sign is alliteration—the repetition of the same letters, words and sounds. This sign is seen in the very early stages before the secondary symptoms, such as autism, delusions, illusions of memory, negativism and catatonic reactions appear, and becomes more exaggerated and more prominent until the schizophrenia is full-blown. The secondary symptoms are seen also in other disorders, but are characteristic of the schizophrenic process.

The general types are: 1. *Chronic schizophrenia* — the catatonic-hebephrenic types, to use the older terminology—is usually mentioned first. I always place a hyphen between "catatonic" and "hebephrenic" because many such patients start out with a typical catatonic psychosis; then the picture changes, so that if the patient were seen for the first time later in the disorder he would be diagnosed as a hebephrenic. There is frequently a shifting back and forth in such cases; they are what I like to call the nuclear

types. The course of the schizophrenic process can be modified in some instances but these cases do not as a rule bear a favorable prognosis.

2. *Simple schizophrenia* or simple dementia praecox—the slowly deteriorating types—actually are not simple cases. They are called "simple" because there are very few colorful symptoms. The patients just sag back, gradually fail in their jobs, and finally sit around, often in the way, at home and may be irritable or exhibit other symptoms that bring them to an institution. A good many may be tolerated at home for several years because they do nothing antisocial. Thus they are complete social and economic misfits, sometimes with a lot of peculiar ideas.

A good many hoboes belong in this class. I used to make something of a hobby of interviewing tramps and found several that could be categorized as simple schizophrenics. These individuals may not have hallucinations or particular delusions but they don't like to work and they don't seem to have much energy. Some may like to talk a little; others are taciturn. Kraepelin agreed with me on the psychology of these individuals. They are chronic schizophrenics who seem to have somewhat different presenting symptoms and constellations.

3. The *schizo-affective type,* in which the emotional components bring the patient into periods of elation or depression, is next in importance. For many years most of these patients were misdiagnosed as manic-depressive because their pressure of speech and presenting symptoms are similar to those seen in true manic-depressive psychoses. The schizo-affective is not influenced so much by the external environment as is the real manic. The content and stimulation come from "inside" their minds. In a good many of the older hospitals and in the large institutions with few staff members, such patients may be classified as manic-depressives and may not be re-examined. After they have had a few swings of emotion, they usually level off into a typical schizophrenic psychosis. Every subsequent psychotic episode will become more pronounced.

Before the advent of electroshock and insulin, and later, the more modern treatments, we used to wonder whether such patients had enough emotion available and expressible to enable them to recover; if such were the case the prognosis, at least for the immediate attack, was somewhat better. If they were true schizophrenics we expected them to come back later and they did.

4. *The paranoid types.* There is an increasing tendency, in a catatonic-hebephrenic setting, to interpret psychotic symptoms as "paranoid." If the patient shows hate, projection or "meanness," he is classified as paranoid. The true paranoid reaction, however, is very different. I don't believe in the modern classification that throws all paranoids and all schizophrenics together. They are different physiologically, as can be demonstrated in the clinic, the laboratory and on the autopsy table. In the real paranoid the physical constitution is more adequate for action and survival.

5. *The neurotic overlay* or mixture may often lead to a diagnosis of psychoneurosis until the patient becomes obviously schizophrenic. In all these pseudoneurotic patients the primary schizophrenic symptoms of Bleuler underlie the neurotic layer. If symptoms do not subside the process will progress to full-blown schizophrenia.

6. The *acute turmoil* type of reaction, which may come in the middle of a

schizophrenic episode, is still another type of prognostic significance. In cases of the acute confusional type the patient may recover from the psychosis and may remain in remission indefinitely. The acute turmoil type is seen in the army and also in civilian life. Some young men who had been emotionally predisposed and were precipitated into military situations of severe stress had terrific turmoil psychosis for a couple of months, then recovered, were sent back home, and discharged. Such symptoms may represent a "therapeutic" psychosis, because in these cases the lid is blown off and the patient gets rid of a mass of repressions. In a few cases it seems that recovery is permanent.

How are we going to select these cases for experiment? Some patients look much older and others appear younger than their chronological ages. There must be some differences in physiology. There are other, more important signs of disturbances in physiology. These may occur in the neurophysiological field alone or may be involved in the metabolic, endocrine or other physiology of the organs that support the brain. There seems to be in these people what one might call a physiologic "clumsiness," that renders the subject intolerant to stress. It would seem to me that the prodigality of effort required by the patient for his attempts at organic adaptation leaves him with inadequate energy for any successful adjustment to society. These people all seem to have less energy than the so-called normal individual.

In the study of schizophrenic children we found that in the lower grades of school they had not participated in sports and had been more or less seclusive but often compensated by becoming good students. They were interested in sports and contests at first, but were awkward and tired easily. They were left out because, although they tried, they were not good team mates. They lacked energy and were unable to function like the others.

One thing more. Case histories, taken by different people, are often full of gaps. We cannot always be sure of the accuracy of the information on the patient. Opinions instead of facts and observations may have been recorded. The chronology is confused. Inadequacy in history-taking is a handicap to the therapist.

Well trained ward personnel should study the patient before preliminary admission to an investigational group. The people who observe the patients daily over a length of time will see many things that the periodic interviewer will miss. Both types of observation are important.

Whether the chronic schizophrenic has been an "in and outer" or whether he has had an uninterrupted hospitalization influences the classification of the patient and the treatment results. From a superficial viewpoint the pseudoneurotic schizophrenic is not severely psychotic, yet he is one of the most resistant to any form of therapy known at the present time.

I don't know what reactions to drugs may be expected in the different types of schizophrenia. But I think such reactions are based on physiological and other constitutional differences of some kind. A strictly psychogenic explanation is not enough.

The whole problem comes down to two or three fundamentals. We have to look for the pathogenic factors in the constitution of the individual, and to differentiate them from the pathoplastic factors—the precipitating and perpetuating events. The precipitating

factors are often only temporary; e.g., grief over death, worry over financial failure, suffering from physical injury, or some other acute stress. The perpetuating factors may be present in the environment.

The prognosis for the individual with an acute breakdown, in which the precipitating factor is an exogenous one, and the physical and laboratory examinations disclose nothing significant, is better than it is for the extremely asthenic patient whose mental symptoms have developed slowly, and who appears to have been predisposed to mental disintegration by tuberculosis or some other debilitating disease. These patients have very little energy to meet even ordinary stresses of life.

DISCUSSION

Dr. Nathan Kline: I was following Doctor Lewis closely to see if he agreed with a report that was issued by the World Health Organization's study group on schizophrenia and published last year (*American Journal of Psychiatry*). I was a co-author of this report, along with Sir Aubrey Lewis of the Maudsley, von Beyer from Germany, Gozzana from Italy, Delgado from Peru, and others from various parts of the world.

There is a strong area of agreement with what Dr. Lewis has said. This is pretty much the current opinion of many of us. I would like to read one statement from the WHO report that came up frequently in the course of the week we spent in formulating this report: "Differences of opinion about the diagnosis of individual patients turn more often on neglect of careful, skilled examination, summary inferences from meager findings, and misunderstanding of the value and limitation of verbal expression, than upon differences of opinion about what schizophrenia is or how it should be diagnosed." We point out that many people are so concerned with psychodynamics that they never bother to make a diagnosis or do a careful examination.

There is a large area of agreement about the nature of the condition known as schizophrenia. Whether or not it constitutes a single disease entity is debatable; Bleuler states in his classic monograph "Dementia Praecox or The Group of Schizophrenias" that he believes the schizophrenias are a "group of diseases," by his own analogy, parallel to the organic brain diseases. Whether one postulates a unitary cause has a great deal to do with the problem of treatment and the use of drugs.

My personal opinion is slightly different but not much at odds with that of Dr. Lewis. I would hold that there is a metabolic defect involved but that there are a number of ways in which this metabolic defect can be precipitated. The precipitant may be an exogenous toxic condition, which was Kraepelin's original postulation; some psychogenic disturbance, or an environmental stress.

A great game in psychiatry is attempting to trace down specifically what this metabolic defect is. I believe that one of our great difficulties in attempting to identify it is that the instrumentation and the procedural technics for identifying long term chronic disorders are not fully utilized. The opinion of my colleague, Dr. Saunders, and myself is that this metabolic defect probably involves an enzyme system. Possibly the presence or absence of those chemicals that speed up, slow down or cause changes in enzyme reactions are crucial to treatment.

I suspect that a whole group of disorders, at present vague, general and unidentifiable, some day will be clearly identified as diseases that fall within this enzyme group.

This raises the neat question as to what the drugs are doing. My private practice includes editors of magazines, writers and other odd characters who ask the most embarrassing questions. One of the questions that invariably comes up is, "Now tell me, Doctor, how does this drug work?" I usually take refuge in the fact that we don't know how most of the drugs in medicine work anyhow, and point out that the mechanism of action of even aspirin or morphine is not understood. The fact of the moment is that we have a number of theories but little concrete knowledge.

I don't even know whether some of the observations about which I belabored Dr. Tislow earlier today have any relevance whatsoever; i.e., some of the biochemical and the pharmacological findings. One drug may elicit a positive response in one patient but not in another. Some have responded to the Rauwolfia alkaloids who obtained no effect from the phenothiazine derivatives, and in others the

reverse has been true. In some patients a combination is necessary. There are patients who will respond to one phenothiazine agent and not to another. Whether the response occurs as a result of the substitution of an acetyl group for a chlorine atom is a very difficult question to answer.

We are laboring in two areas at the same time. We are looking at the biochemical-pharmacological area and simultaneously at the psychological area. The relationship between these two fields is unclear. Sometimes observers attempt to jump from one to the other without defining what the relationship is. They will say, for instance, that the cause of delusions of grandeur, forgetfulness and a few other symptoms, such as occur in syphilis, as Dr. Lewis mentioned, is arteriolar cuffiing, or loss of cells in the frontal lobe. It may be that there is some relationship between the two, but why these specific areas of pathology should lead to delusions of grandeur has not been explained.

The same problem exists in relation to the chemistry of the biological area. Even after we discover the presence of, or identify, as we hope to, certain definite biochemical pathology, we still have not answered the question of why such disturbance should produce loosening of the associations and other symptoms that Kraepelin and Bleuler described.

The contribution we shall make this afternoon, when Dr. Saunders holds forth, will add at least to the confusion, if not to the knowledge of the subject. There are actually times when confusion has its value. As long as we think we know how things work we are not apt to become disturbed about them. If we find that the area is confused and that we are contradicting one another, we usually attempt to resolve the problem.

In our presentation we have taken the primary and secondary symptoms, which Dr. Lewis has so kindly summarized for us, and attempted to determine how each is affected by the various phenothiazine compounds and by the psychic energizers. We feel that it is possible in this way to extend the differential choice of drugs on a clinical basis. The hope that the drugs themselves will differentiate for us the various types of schizophrenia has not been lost. No one has yet carried out a systematic study in this area: by taking, for example, patients who respond to one phenothiazine agent and not to another, or to a Rauwolfia alkaloid and not to a phenothiazine derivative, and differentiating them clinically. It would be particularly valuable if the response to therapy could be predicted. We have been running a project for a number of years involving an "interaction chronograph," which is based on interview patterns—not the content but the form of response to a standard interview. On the basis of these indications we have been fairly well able to predict which drugs would have what effect.

About four or five years ago I wrote a paper with Ostow that attempted to provide a psychodynamic theory of why the ataractic drugs work. Our theory was that the phenothiazine compounds and the Rauwolfia alkaloids functioned by reducing the amount of psychic energy in the individual; that hallucinations or delusions usually develop in the schizophrenic individual (if you wish to resort to analytic terminology, there is an id thrust). Something comes from the unconscious that demands expression. The individual is incapable of channeling such forces in generally acceptable form and therefore pathological hallucinations, illusions, and other symptoms develop.

Administration of phenothiazine compounds or the Rauwolfia alkaloids reduces the total amount of energy available to the individual and because the drive behind such unacceptable id impulses is lessened, he is able to constitute himself again. In this way the secondary symptoms of schizophrenia disappear.

When the psychic energizers were introduced, we found that these agents did exactly the opposite; that is, they increased the drive. We learned to our dismay that administration of such compounds to schizophrenic patients either made the disorder much worse or precipitated frank schizophrenia where formerly it had been latent or at least not much in evidence. However, we found that combination of the energizers with the ataraxics did something about which Dr. Saunders will speak this afternoon. That is, such combination altered the primary symptoms of schizophrenia, something we rarely had been able to achieve with the phenothiazine derivatives alone. Reserpine, on the other hand, functions in the opposite direction, since it accentuates the effect of the psychic energizers.

Carphenazine in the Treatment of Schizophrenia

JANE E. OLTMAN, M.D., and SAMUEL FRIEDMAN, M.D.

The present study is concerned with evaluation of a new ataractic drug, carphenazine, from the standpoint of its intrinsic efficacy in the treatment of schizophrenia, and additionally with respect to its relative value as compared to perphenazine.

We have been using carphenazine and its earlier analogue for approximately a year. The clinical material for this study has been homogeneous in one respect; it consisted entirely of female schizophrenic individuals. The major portion of the study included patients newly received on the female admission service. In addition, another small group of 16 chronically ill female patients was treated. These had been ill for many years, and had been hospitalized for periods ranging from three to 31 years, with a median of 19 years. They had been unsuccessfully treated with the usual gamut of somatic therapies, including some or all of the following: electroshock, insulin coma, lobotomy and a variety of ataractic drugs. Dosage of carphenazine for this group was increased progressively from 100 mg. daily to 450 mg. daily, by weekly increments of 50 mg. during a total treatment period of eight weeks. The results of treatment in this group of patients were essentially negative. Some degree of mild behavioristic response was noted in a few but significant improvement was lacking. Side effects were moderate, particularly in view of the large doses employed. Parkinsonism, usually of mild degree, was apparent in five cases, including one with oculogyric crises, and one patient exhibited moderate akathisia. It may be concluded, therefore, that this compound, like the other ataractic drugs that preceded and followed it, was essentially ineffective in this group of "hard core" schizophrenics, except for some reduction of behavioristic difficulties.

The more significant portion of this study was devoted to patients newly admitted to the hospital. They represented a typical cross section, and longitudinal section as well, of schizophrenia. Their illnesses were in general of more recent origin, although here, too, in some instances, chronicity was already well established. These patients ranged in age from 14 to 62; however, almost two thirds were in the third and fourth decades of life. The total duration of illness varied considerably—from a few days to 31 years. The duration of the present illness was as follows: less than one year, 48 per cent; one to two years, 21 per cent; more than two years, 31 per cent. This represented the first hospitalization for approximately half of the patients.

There were 107 individual patients in this group, but 149 separate treatment periods were available for comparison as follows: perphenazine, 44; placebo, 18; and carphenazine, 87. A treatment period consisted of at least four weeks of therapy. Dosage of carphenazine ranged chiefly from 50 to 150 mg. daily; and of perphenazine, from 16 to 48 mg. daily. Initially, attempt was made to rotate each patient through each of the three phases of treatment; however, a number of difficulties were encountered in this program. Later, patients were assigned to treatment with each of the active drugs by chance rotation, with the exception that those who refused to

From The Fairfield State Hospital, Newtown, Conn.

take medication orally were assigned to the perphenazine group. The drug used was unknown to one of the authors. The level of improvement was assayed by clinical evaluation only; it was guided by an objectivity based on many years of psychiatric experience.

The overall results are summarized in Table 1. It is apparent that both active drugs were significantly more effective than the placebo ($p=<.01$). This is similar to the result recently reported[1] in a comparative study of several phenothiazine compounds and placebo in a large series of cases. The results with perphenazine also appear comparable to those previously reported by Goldman.[2] The efficacy of the two active drugs appears to be fairly similar. There is a slightly higher A level of improvement with perphenazine, whereas carphenazine is somewhat more effective when both A and B levels of improvement are considered ($p=<.02$). Cases in which both drugs were used in tandem or during separate episodes of illness exhibited congruous results. Thus in 12 instances, both drugs were unsuccessful; in four cases both effected a much improved level; in three instances of failure with perphenazine, carphenazine produced an A level of improvement; and in two instances of failure with carphenazine, perphenazine effected an improved and much improved level. It may be concluded at this point, therefore, that carphenazine is an effective ataractic agent for the treatment of schizophrenia, with approximately the same range of efficiency as perphenazine. One deficiency with respect to carphenazine was its relative unavailability in other than oral form.

More detailed analysis of the factors that contributed to successful results indicated a similar pattern for both

TABLE 1

Results of Therapy with Carphenazine, Perphenazine and Placebo

Drug	Number of Treatment Periods	Level of Improvement A No.	%	B No.	%	C No.	%
Carphenazine	87	36	41	25	29	26	30
Perphenazine	44	21	48	4	9	19	43
Placebo	18	2	11	4	22	12	67

A—In remission or much improved
B—Improved
C—Slightly improved or unimproved

drugs, with identification of features that have long been recognized as hopeful prognostic criteria in dementia praecox. One of these was the duration of the present illness. Here we find that 60 to 65 per cent of those patients whose illness was less than one year in duration achieved an A level of improvement, whereas this figure dropped to approximately 25 per cent in instances in which the illness was of more than two years' duration. Phrased in a slightly different frame of reference, it was revealed that in approximately 80 per cent of drug-treated patients who exhibited an A level of improvement, the illness was less than one year in duration. Conversely, of those who showed negligible improvement, 64 per cent had an illness of more than two years in the case of carphenazine, and 56 per cent in the case of perphenazine. Thus, the conclusion is inevitable that duration of illness is an important qualifying factor, a situation well recognized in the past.

The type of onset and the reaction of the patient also have been regarded as prognostically significant. Analysis of this area showed that some 70 per cent of patients whose onset was relatively acute and whose reaction might be termed a vigorous one, achieved an A level of improvement. On the other hand, only 20 per cent of patients with

an insidious type of onset and a passive, constricted, nonvigorous type of reaction attained a similar level of improvement.

A related feature is concerned with the type of symptomatology. There was well defined clinical observation to the effect that patients who were experiencing active delusions and hallucinations, acute feelings of unreality, ideas of reference and projection phenomena, particularly if these were associated with a sense of impending danger or catastrophe or a panic reaction, responded well to drug therapy. On the other hand, patients whose thought processes were characterized by rather diffuse fantasies, feelings of inadequacy or inferiority, vague gropings toward an ill-defined goal, expressions of unrest or lack of success or of interpersonal difficulties with members of the family or employers, exhibited much less satisfactory results. Although it was more difficult to subject this area to statistical analysis, we found that some 75 per cent of patients who exhibited the first type of symptoms achieved an A level of improvement whereas approximately 65 per cent of the second group showed negligible improvement under drug therapy. In several instances, some degree of behavioristic improvement was observed under placebo therapy only; however, auditory hallucinations failed to subside until carphenazine or perphenazine was added to the therapeutic program. Subsidence of the hallucinatory features was then usually quite prompt—frequently within a matter of a few days. Thus in many instances both carphenazine and perphenazine appeared to have almost specific antidelusional and antihallucinatory effect. However, this effect was certainly less prominent when the delusions were chronic, or somatic in nature.

The following abbreviated case histories illustrate the type of illnesses in which drug therapy was most effective.

Case 1. D.K., a 31-year-old married woman, was hospitalized on December 5, 1959. Mental abnormalities had begun about a month after the birth of her third child in September. At first she complained merely of excessive fatigue and vague somatic difficulties. Soon, however, she became apprehensive, expressed fears of being left alone at night and begged her husband, who had recently been shifted to night duty, to absent himself from work and stay home with the family, as she was terrified that some intruder would kill her or the children. On one occasion, she said to her husband, "Go on out and kill yourself as you're going to die anyway." On another occasion, she gathered up her children at 4 a.m. and fled to her sister-in-law's home for safety.

After her admission to the hospital she appeared tense and apprehensive. She elaborated on the delusions as described, stressing her fixed belief that some member of her family was going to be killed. She recalled that on one occasion she ran to school, fearful for her son's life. Various innocent situations had become portents of evil to her. A blue dress hanging in her closet had signified to her the imminent death of her husband.

The diagnosis of schizophrenic reaction, acute undifferentiated type, was made. She improved promptly under carphenazine therapy (50 mg. three times daily) and was able to leave the hospital within five weeks. Examinations in the outpatient clinic during the succeeding eight months showed good maintenance of her satisfactory status.

Case 2. A. C., a 33-year-old married woman, was admitted to the hospital on January 18, 1960. Her psychosis had begun about a month or two prior to admission, with onset of auditory hallucinations. She would wander repeatedly through her house, seeking the source of the voices. She was insomniac, and got up frequently at night to reassure herself about her children. She expressed the delusion that someone was trying to abduct them and that her own life was in danger.

In the hospital she appeared anxious, retarded and confused; she stated that the omnipresent voices accused her of neglecting and rejecting her children. She had suspected the

presence of an evil intruder in her home. There were vague self-accusations.

The diagnosis of schizophrenic reaction, schizo-affective type, was made. The hallucinations and fears subsided rapidly under carphenazine therapy (50 mg. three times daily), and the patient was released within a month, without further medication. She was readmitted three weeks later, again anxious and hallucinated. Renewal of carphenazine therapy resulted in prompt improvement, and she was again discharged in 32 days. Under maintenance medication her satisfactory status has continued.

Case 3. H.B., a 40-year-old married woman, was admitted to the hospital on February 16, 1960. She had suffered from a skin eruption, apparently a neurodermatitis, for several years. Finally, about six months prior to hospitalization, she consulted a psychiatrist. Tranquilizers were prescribed, with relatively little success. Admission was necessitated by an acute psychotic episode in which she was anxious, fearful, insomniac and hallucinated.

On arrival at the hospital, she was tense and apprehensive, and stated that she wanted all her clothes burned so that she could start life anew. During interviews she described a number of bizarre phenomena. She stated that one night, while watching a television program about a seeing-eye dog, she suddenly felt that she was a dog. She heard voices, chiefly those of her father and the psychiatrist who had attended her, and strange, clicking figures appeared before her. She experienced a terrified, confused feeling, and the sensation that "something was closing in on me." She was apprehensive of her husband who seemed to loom before her in a threatening guise.

The diagnosis of schizophrenic reaction, acute undifferentiated type, was made. She appeared to improve somewhat under placebo therapy, but the underlying anxiety and hallucinations persisted. These features disappeared within a week after administration of carphenazine (25 mg. three times a day). She was discharged one month thereafter, with maintenance drug therapy (25 mg. twice daily). Satisfactory status has been maintained.

Case 4. M.L., a 47-year-old married woman, was admitted on January 9, 1960. About two years previously she had suffered a psychotic episode in which she was apprehensive and expressed fears of being alone. She voiced the delusion that her son was kidnaped and she sought assistance from the police. She received a course of electroconvulsive therapy with satisfactory improvement but approximately one year later her psychosis recurred. She expressed numerous delusions to the effect that she was the subject of discussion on a television program, that the neighbors were in league against her and that they tape-recorded her thoughts and conversations. She kept her door barricaded and finally she was arrested for assaulting a repairman who tried to enter her home.

In the hospital she expounded readily on all her paranoid ideas. She spoke of sound waves in her apartment which were transmitted to the television set and then reflected back to her. Her neighbors were attempting to scandalize her, and had televised her entire past life. People were gossiping about her, writing books about her under fictitious names, and attempting to run her and her husband out of town. She, in turn, had certain powers to combat them as she was "gifted and guided."

The diagnosis of schizophrenic reaction, paranoid type, was made. Carphenazine was initiated in dosage of 25 mg. three times a day and later increased to 50 mg. three times a day. Progressive reduction of her delusional system was apparent in about three weeks, although insight remained limited. She was discharged as much improved seven weeks after admission.

Other factors were of negligible significance. Age did not appear to exert any definite influence, although there was a slight tendency for individuals in the fourth decade of life to exhibit somewhat better results. Sex was not a relevant factor inasmuch as all of the patients in this study were female. Multiplicity of attacks did not appear to be a pertinent factor provided the patient had exhibited satisfactory remissions during the interval periods. In fact, there was some trend for individuals who had had more than three admissions to exhibit more satisfactory improvement. This again was probably merely a reflection of their innate capacity toward remission. History of mental illness in the family did not seem to influence the results in any defi-

nite direction.

Thus, schizophrenic patients who exhibit the greatest degree of improvement under drug therapy, as they do under other forms of psychiatric treatment, are those whose illness is associated with such favorable prognostic signs as: present illness of less than one year in duration, acute type of onset with vigorous emotional reaction, acute hallucinations and delusions, and ideas of unreality, frequently accompanied by anxiety or panic reaction. Those who exhibit least satisfactory response are individuals whose illness is associated with the time-honored unfavorable prognostic criteria, such as: insidiously progressive onset, autistic reaction, illness of two or more years in duration, lack of vigorous emotional reactivity, evidences of general inadequate functioning, and thought processes characterized by vague, ill-defined features such as feelings of inadequacy and frustration or poorly crystallized groping for some nebulous and unobtainable happiness.

It is evident, therefore, that drug therapy is chiefly effective against the so-called secondary symptoms of schizophrenia and that optimal therapeutic results are obtained in acute paranoid reactions and schizophreniform types of illnesses in the schizophrenic axis. Such medication is much less efficacious against the primary features of schizophrenia and the ingrained, nuclear forms of the disease, long represented by the simple and hebephrenic subgroups.

Serious complications were absent during use of both drugs. Liver function profiles and transaminase levels remained within normal limits. Side effects were entirely in the direction of extrapyramidal disorders. In the carphenazine-treated group, parkinsonism appeared in 11 patients, akathisia in eight, and both features in six, for a total of 29 per cent. In the perphenazine-treated group, there were four patients with parkinsonism, one with akathisia, and three with both, for a total of 18 per cent. The parkinsonism was mild in most instances and was readily controlled by appropriate agents.

From the standpoint of subjective disturbance, patients usually complained more of akathisia. One coined a neologistic term for this disorder: she stated the medicine made her "too walkative." Somnolence, when present, was usually also mild, and tended to disappear with the passage of time.

SUMMARY

Evaluation of a new ataractic drug, carphenazine, indicated that it is an effective agent in the treatment of appropriate forms of schizophrenia, with approximately the same range of efficacy as perphenazine. Patients whose illness was relatively acute in onset, less than one year in duration, and characterized by acute delusions, hallucinations, ideas of unreality and vigorous emotional reaction, exhibited the greatest improvement. Side effects, consisting of extrapyramidal features, were generally slight.

Newtown, Conn.

REFERENCES

1. Casey, J. F., Lasky, J. J., Klett, C. J., and Hollister, L. E.: Treatment of Schizophrenic Reactions with Phenothiazine Derivatives; A Comparative Study of Chlorpromazine, Trifluprom azine, Mepazine, Prochlorperazine, Perphenazine and Phenobarbital. *Am. J. Psychiat.*, 117: 97-105, 1960.
2. Goldman, D.: The Results of Treatment of Psychotic States with Newer Phenothiazine Compounds Effective in Small Doses. *Am. J. M. Sc.*, 235: 67-77, 1958.

Use of Carphenazine in Severely Ill Psychiatric Out-Patients

SIDNEY MERLIS, M.D.*

As a corollary to our studies with chronically ill, withdrawn, apathetic psychotic in-patients, we attempted to determine the therapeutic value of carphenazine in an outpatient group. Medication in psychiatry depends for effectiveness on selection of patients suitable for treatment with the agent to be used. However, diagnostic categories in mental illness are vague and ill-defined; investigators are hampered by uncertainty concerning their case material. Psychiatrists do not often agree as to appropriate groupings of patients. Lacking a basic science structure, methods of treatment must be empirically determined. Therefore, treatment may be haphazard and uncertain, and clinical reports paradoxical. Above all, the type of patient to be treated must be clearly defined. The grouping of schizophrenic patients in their various subcategories may look well for statistical purpose but certainly does not imply therapeutic significance.

We know the morbidity and prognosis of the various types of psychiatric diagnoses but we have no treatment that is at all specific for any of them. Psychopharmacology has demonstrated without question that alteration of the clinical picture by drug therapy always cuts across diagnostic lines. Since psychopharmacological agents produce symptomatic effects only, the clinician must determine for himself the action and therapeutic value of the drug to be used. The differences in effect produced by the various agents available are fundamentally variations in degree of intensity rather than differences in action. Thus we have a continuum of psychotropic compounds that produce effects varying from mild to profound. It is the phenothiazine series that concerns us most at present. Even in this group we must deal with compounds that produce mild, moderate or pronounced symptomatic effects.

Carphenazine, a potent phenothiazine derivative, was used in a selected group of 15 out-patients, with a history of chronic mental illness of one to 18 years, to determine the therapeutic value of the compound in producing symptomatic improvement. The series consisted of four males and 11 females, ranging in age from 11 to 56 years, all of whom were living at home. All had been under close observation for a minimum of four months; the available histories of these patients extended back as long as eight years. The case material, dosage and duration of treatment with carphenazine are shown in Table 1. All patients had been treated with numerous psychotropic agents, with varying degrees of relief. Medication with carphenazine was instituted in an attempt to determine whether additional improvement could be obtained. Carphenazine was gradually introduced after slow withdrawal of all previous therapy. Maximum dosage reached 112.5 mg. per day. Patients were seen once or twice weekly for periods of up to seven months. Superficial psychotherapy was used concomitantly with carphenazine.

From the Research Division of Central Islip State Hospital, Central Islip, L. I., N. Y.
*Director of Research, Central Islip State Hospital, Central Islip, L. I., N. Y.

TABLE 1

CARPHENAZINE

Case Material

Pt. No.	Age	Sex	Group Diagnosis	Duration of Illness Years	Maximum Daily Dosage of Carphenazine mg.	Duration of Medication with Carphenazine
1	17	F	Schizophrenia	5	37.5 t.i.d.	45 days
2	11	M	Schizophrenia	11	12.5 q.i.d.	5 mos.
3	12	M	Character Disorder	6	12.5 b.i.d.	4 mos.
4	30	F	Schizophrenia	14	25 b.i.d.	5 mos.
5	56	F	Pseudoneurotic Schizophrenia	18	25 b.i.d.	3 mos.
6	45	F	Schizophrenia	4	25 b.i.d.	6 mos.
7	39	F	Pseudoneurotic Schizophrenia	2	12.5 b.i.d.	4 mos.
8	41	F	Psychoneurosis	1	25 b.i.d.	2 mos.
9	27	F	Psychoneurosis	7	25 b.i.d.	5 mos.
10	19	F	Schizophrenia	3	12.5 t.i.d.	3 mos.
11	46	M	Psychoneurosis	2	25 b.i.d.	7 days
12	35	F	Pseudoneurotic Schizophrenia	3	25 b.i.d.	3 mos.
13	35	F	Psychoneurosis	2	12.5 t.i.d.	4 mos.
14	45	F	Pseudoneurotic Schizophrenia	2	12.5 b.i.d.	3 mos.
15	37	M	Schizophrenia	8	25 q.i.d.	7 mos.

Gradations of clinical improvement were determined as follows:

1. "Pronounced improvement" indicated that the patient became relatively asymptomatic after treatment.
2. "Moderate improvement" indicated significant relief of the patient's complaints.
3. "Slight improvement" consisted of little more than partial relief.
4. When signs of improvement were questionable or minimal the response was classified as "unchanged."

Although the material in this study represented several diagnostic categories, the clinical history was similar in all cases and can be described as follows: The patients maintained a tenuous psychological status. They lived at home with relatives who were sympathetic and, for the most part, understanding. The patients had some degree of motivation for relief of symptoms, or as they described it, "cure," for which they were willing to continue under psychiatric care with little or no urging. All were intelligent. The majority maintained themselves in occupations considered significantly below their intellectual capacities. Most were employed in menial labor; many of the housewives in the group received a great deal of active aid from their husbands and children. The psychiatric pattern was often cyclic; the patients responded to relatively minor trauma with exaggerated emotional swings. The pattern of existence was rigid, with little attempt toward new experiences. They avoided unpredictable contacts as much as possible. In a superficial relationship, such people might appear normal in all respects. Their basic psychological conflicts were easily apparent to a trained eye; under continued observation a severe psychological disorder was detectable. In times of stress

their capacity for stability was limited and they were continuously on the edge of emotional decompensation. Our overall therapeutic results in this particular group were quite encouraging. The effects of medication were often perceptible within the first week. Three patients showed pronounced, five moderate and two minimal improvement; five patients showed no change (Table 2). Again, the effects crossed all diagnostic boundaries and no evidence could be detected of therapeutic response in any one specific group. Although all patients retained their central core of basic psychological disability, the overt behavior patterns appeared altered. There were visible evidences of decreased anxiety. Several patients appeared more outgoing and there were some exceptions to the rigid pattern of their everyday routine. Their activities became more effective and they showed an increase in calmness.

Most patients complained of sedation in the initial period of medication. Three showed significant side effects. One of these was forced to discontinue treatment because of extreme drowsiness. Another also had significant sedation but continued treatment for 60 days, after which her visits ceased; she was considered unimproved. Parkinsonism developed in the third. This patient had received a maximum dosage of 100 mg. per day, which level was reached in gradually ascending doses. Her extrapyramidal symptoms responded to Artane®, 6 mg. per day, and medication with this combination was continued with good clinical effect.

TABLE 2

CARPHENAZINE

Results of Treatment

Diagnosis	No. Patients	Pronounced Improvement	Moderate Improvement	Minimal Improvement	No Change
Schizophrenia	6	2	3	0	1
Pseudoneurotic Schizophrenia	4	1	1	0	2
Psychoneurosis	4	0	1	1	2
Character Disorder	1	0	0	1	0
Total	15	3	5	2	5

SUMMARY AND CONCLUSION

As could be expected in this type of patient, the response to treatment was significant in comparison with the results of our study in chronic hospitalized schizophrenics. Although one cannot always be sure that alterations in the clinical picture result from the medication alone, the effects, at least in this group, who had been under rather prolonged observation, would seem most likely to be attributable to carphenazine. Side effects were relatively unimportant, and were often absent during therapeutically effective medication in the low dosage range, particularly if the compound was administered in gradually increasing amounts.

Carphenazine appears to be a useful and relatively safe agent and is suitable for treatment of certain nonhospitalized patients.

DISCUSSION

Dr. Saunders: What was the incidence of severe sedation?

Dr. Merlis: In only one instance was drowsiness severe. In the other cases sedation was mild. This we were able to control to a large extent by administering the medication in late afternoon or evening. The patients usually became accustomed to the effects of the compound in a week or so.

Dr. Goldman: Were you able to control the intake of the medication in out-patients?

Dr. Merlis: No. This is one of the greatest problems with treatment of out-patients. We carefully counted the number of tablets

handed out when we supplied the medication. The patients were told to return at a certain time and if they came back empty-handed we assumed they had taken the tablets. Whether they actually did or not we couldn't say. We had an in-patient who received 10 Gm. of chlorpromazine a day. She evaded swallowing of the dose and stored the drug in a pillow case.

Dr. Friedman: Was there any relationship between the diagnostic category and the occurrence of significant improvement?

Dr. Merlis: No.

Dr. Friedman: I noted that you used 150 mg. a day for the males in your chronic population, in contrast to the 450 mg. dosage used for the females in our series. The results for both groups were similar. I think that if patients are going to improve they will do so on fairly moderate doses. Pushing the dosage to tremendous amounts probably will not increase the degree or the incidence of improvement.

Dr. Merlis: I would be inclined to agree.

Dr. Page: I think this is a very important point. Once you have obtained improvement, if you increase the dose does anything further happen?

Dr. Goldman: With chronic patients particularly, the dose must be increased to the point at which significant improvement or excessive side effects occur.

Dr. Merlis: This is probably so in some cases but I don't think you can make a general statement that by merely raising the dose for a given group of patients you will get a predictable response.

Dr. Sainz: By giving merely a minimum dose you may obtain improvement in patients who would have improved anyway; if you do not administer larger doses you will fail to benefit those who could have been improved on increased dosage. This is not a matter of speculation. Two years ago we published the results of controlled studies on patients receiving psychotherapy and on patients receiving minimum doses of medication. Then we treated all the failures intensively, and obtained improvement in 75 per cent.

A Comparison Between Trifluoperazine and Carphenazine in Chronically Ill Schizophrenic In-Patients

J. CACIOPPO, M.D., H. BABIKIAN, M.D.,
and SIDNEY MERLIS, M.D.*

Among the many psychotropic compounds available today, several have been suggested as having particular effectiveness in chronically ill schizophrenics who have been noticeably resistant to previously available therapy. Claims of markedly high potency and effectiveness from relatively low dosages have been made for these compounds. A major obstacle to clinical use of such agents has been the high incidence of side effects. Such disturbances can affect more than 50 per cent of the patients treated.[1-4] Extrapyramidal symptoms are by far the commonest. There has been continued effort to find a therapeutically effective agent for the chronic mental patient that lacks the risk of frequent side effects, as currently seen with available compounds. In this study the clinical response to trifluoperazine was compared to the response to carphenazine, with special reference to the side reactions elicited.

The series included a total of 50 male patients varying in age from 21 to 59 years, with a history of mental illness ranging from two to 33 years (Table 1). They had been selected from the continuous treatment services, and had been hospitalized and under continued observation for a minimum of three years. Their behavior patterns and response to other forms of psychiatric therapy had been carefully assessed, and they were considered unresponsive to all other available treatment. Because, in psychiatric research, the nature of the clinical material is particularly important for intelligent evaluation of the effectiveness of a treatment, a few comments regarding the specific syndromes manifested by our experimental group seem appropriate.

The over-all clinical picture was that of apathy, lethargy and withdrawal. The patients avoided social contact and preferred to be isolated from their environment. Their responses to external stimuli were markedly reduced. Communication was limited. Efforts to approach them were usually met with hostility and resistance. Intrusion into their limited habitual activity patterns often led to aggressive outbursts of behavior directed immediately against the interviewer or subsequently against some inanimate object: they would throw chairs, pace constantly or break windows.

Their dress was usually slovenly, and their eating habits poor, with wide extremes of food intake. Dietary management ranged from the need of forced feeding to strict limitation of the diet because of bulimia. Resistance to medication was frequent, and varied from gross refusal to subtle hiding and subsequent disposal of the tablet. Few patients, if any, complained of illness. The relatively acute syndromes were recognized objectively; most symptoms, however, were overlooked or ignored by the

From the Research Division of Central Islip State Hospital, Central Islip, L. I., N. Y.
*Director of Research, Central Islip State Hospital, Central Islip, L. I., N. Y.

TABLE 1

Case Material

Initials	Age	Sex	Duration of Illnes—yrs.	Diagnosis Schizophrenic Subtype	Initials	Age	Sex	Duration of Illness—Yrs.	Diagnosis Schizophrenic Subtype
S.A.	48	M	7	Catatonic	G.A.	51	M	17	Hebephrenic
P.A.	45	M	7	Hebephrenic	G.B.	46	M	18	Paranoid
J.A.	46	M	23	Hebephrenic	M.B.	45	M	17	Hebephrenic
P.B.	48	M	15	Paranoid	U.B.	35	M	7	Hebephrenic
J.C.	49	M	5	Hebephrenic	L.C.	51	M	20	Hebephrenic
G.C.	44	M	27	Paranoid	J.D.	47	M	25	Paranoid
R.C.	43	M	23	Hebephrenic	E.C.	47	M	11	Catatonic
R.D.	46	M	17	Catatonic	E.F.	47	M	24	Paranoid
L.E.	56	M	33	Catatonic	A.G.	49	M	15	Hebephrenic
W.E.	59	M	27	Catatonic	M.H.	50	M	14	Mixed
H.F.	49	M	24	Paranoid	J.I.	56	M	31	Hebephrenic
E.F.	45	M	6	Hebephrenic	A.J.	48	M	18	Paranoid
W.H.	56	M	33	Hebephrenic	W.K.	51	M	27	Catatonic
T.H.	46	M	24	Hebephrenic	A.L.	46	M	28	Hebephrenic
V.I.	54	M	18	Hebephrenic	C.L.	57	M	5	Paranoid
J.K.	41	M	8	Paranoid	L.P.	46	M	22	Paranoid
F.K.	38	M	4	Hebephrenic	T.P.	43	M	22	Catatonic
B.L.	50	M	7	Hebephrenic	R.R.	21	M	2	Hebephrenic
M.L.	44	M	27	Hebephrenic	J.S.	44	M	22	Hebephrenic
F.M.	29	M	7	Catatonic	S.S.	44	M	23	Paranoid
M.N.	42	M	2	Catatonic	R.M.	37	M	18	Catatonic
I.R.	40	M	26	Paranoid	C.M.	49	M	22	Paranoid
H.S.	52	M	33	Paranoid	F.M.	47	M	3	Hebephrenic
W.T.	47	M	2	Paranoid	N.N.	52	M	30	Catatonic
M.B.	57	M	29	Mental deficiency (not schizophren.)	G.S.	48	M	12	Paranoid

patient. There was no perceptible motivation for improvement.

Baseline medical and laboratory examinations done prior to this study disclosed no evidence of systemic pathology. Patients were observed two to three times weekly by a team of psychiatrists, nurses and attendants, and were individually rated. Routine interviews and stereotyped questions were avoided. Psychotherapy was not given intentionally. The ward environment was unchanged. The patient routine remained the same. The only alteration, therefore, was the introduction of medication and periodic routine laboratory procedures, which included complete blood counts, urinalyses and liver function studies.

The criteria for evaluating the response to treatment were based primarily on objective improvement as observed by the staff. When changes in this series were questionable, they were recorded as "no improvement." A grading of "slight improvement" indicated some degree of alteration in behavior, which enabled the patient to be more self-sufficient, less antisocial and less of a management problem. The patient was considered to show "moderate improvement" when behavior and appearance became less overtly psychotic, his capacity for expressing himself was in-

creased and he became able to carry on a conversation with some degree of continuity and logic. If all symptoms of illness disappeared, the response was considered "pronounced improvement." A patient who achieved this category would be suitable for discharge.

The 50 patients were equally divided at random into two groups, one of which received trifluoperazine and one, carphenazine. As tablet medication was started, one patient in the carphenazine-treated group refused therapy. He was immediately started on trifluoperazine, 1 mg. intramuscularly once daily, and continued on intramuscular therapy throughout the study.

A second patient who received carphenazine abruptly refused to continue after 3½ weeks of treatment. He was immediately shifted to trifluoperazine intramuscularly in doses of 1 mg. once daily, and continued under treatment in the trifluoperazine group until the end of the study. Thus, the final grouping consisted of 27 patients who received trifluoperazine, and 23 who received carphenazine.

Trifluoperazine was supplied as 5 mg. tablets; carphenazine, in tablets of 25 mg. All patients were started at the same time and given one tablet daily for three days. The dose was then increased to two tablets daily for four days. For an additional seven days the patients received three tablets in divided doses. By the beginning of the fourth week the daily dose of trifluoperazine was 20 mg., and of carphenazine, 100 mg.

At this time significant and disturbing side effects developed in 19 of the 27 patients receiving trifluoperazine, and the dose was reduced to 15 mg. per day. These side reactions were primarily those of the Parkinson-like syndrome, akathisia and sedation. The dose of carphenazine was progressively increased until a maximum of 150 mg. per day was administered. These dosages were continued until the end of the study. The total duration of the investigation was 15 weeks. Actual treatment was conducted for nine weeks, and the pre- and post-treatment observations were continued for three weeks each. This study was designed to assess the therapeutic effects of the two compounds as well as to evaluate the frequency of side effects with regard to the dose level employed.

Eight of the carphenazine-treated and eight of the trifluoperazine-treated patients showed some degree of improvement. The clinical change was not pronounced and comparison of the results obtained in both groups shows that there was no practical difference between the effects of the two agents (Tables 2 and 3). No diagnostic category was particularly affected; improvement was rather generally dispersed.

Four patients showed slight improvement, and four moderate improvement under carphenazine medication whereas five showed slight improvement and

TABLE 2

Summary of Therapeutic Response to Carphenazine

Diagnosis Schizophrenic Subtype	Total No. of Patients	Moderate Improvement	Slight Improvement	No Imp'v't or Worse
Catatonic	6	1	1	4
Hebephrenic	9	0	3	6
Paranoid	7	3	0	4
Mental Deficiency, Confusion*	1	0	0	1
Total	23	4	4	15

*Not schizophrenic.

TABLE 3

Summary of Therapeutic Response to Trifluoperazine

Diagnosis Schizophrenic Subtype	Total No. of Patients	Moderate Improvement	Slight Improvement	No Imp't or Worse
Catatonic	5	0	1	4
Hebephrenic	12	0	2	10
Paranoid	9	2	2	5
Mixed	1	1	0	0
Total	27	3	5	19

three moderate improvement with trifluoperazine. One patient was considered to have been made worse with carphenazine and three seemed worse with trifluoperazine. The remainder showed no significant response. The number of unimproved patients was quite extensive in both groups.

Side Effects

Both drugs produced disturbing side reactions (Table 4). Lethargy occurred in five during carphenazine medication and in seven with trifluoperazine. Parkinsonism was seen in five during carphenazine treatment and in three with trifluoperazine. Lethargy tended to diminish after a few days of carphenazine medication. The dose of carphenazine was then raised with recurrence of excessive sedation in only a few patients. Pronounced agitation and increased confusion occurred in one patient taking 25 mg. per day with an over-all accentuation of the clinical syndrome. Carphenazine was discontinued for this patient after six days.

TABLE 4

Side Effects	Carphenazine		Trifluoperazine	
	No. of Patients	Aver. Dose at Which Effect Appeared mg.	No. of Patients	Aver. Dose at Which Effect Appeared mg.
Lethargy*	5	25–150	7	5–20
Parkinsonism	5	125	3	15
Weight loss†	4	25–150	9	5–20
Physically ill			3	15
Disturbed	1	25		
Liver damage	2	150	4	15

*Lethargy and weight loss appeared throughout course of the study.

†Weight loss varied from 9 to 29 pounds.

Nausea, vomiting and malaise developed in three patients during trifluoperazine medication. For these the compound was discontinued after six, seven and fifteen days, respectively. Liver dysfunction, although not extensive, was sufficiently disturbing to cause discontinuation of therapy in two patients receiving carphenazine and four receiving trifluoperazine.

SUMMARY

Fifty chronically ill male psychotic patients were studied to determine the comparative therapeutic effects of trifluoperazine and carphenazine and to consider the significance and extent of side effects. For chronically ill psychotics who show apathy, dishevelment, untidiness, confusion, disinterest, and similar basic symptoms, carphenazine and trifluoperazine appear similar in action. Little distinctive difference could be elicited in this study. Percentagewise, however, the incidence of improvement under carphenazine was somewhat higher than the improvement with trifluoperazine.

The margin of safety, defined as the difference between the dosage level at which a therapeutic effect is obtained and the dosage at which significant toxicity occurs, is definitely different. Carphenazine permitted a wider adjustment in dosage to meet individual requirements than did trifluoperazine.

In no case was it possible to administer more than 20 mg. of trifluopera-

zine without distressing effects in some degree. With carphenazine, greater leeway was available in the therapeutic range so that the dose could be adjusted more easily. Thus carphenazine had a wider margin of safety than trifluoperazine. Therapeutic effects were often obtained in the patients who responded to carphenazine, with daily doses ranging from 50 to 75 mg.; doses of less than 100 mg. per day rarely elicited significant side effects.

DISCUSSION

Dr. Kline: What kind of liver changes were seen?

Dr. Merlis: Cephalin flocculation findings of 3 plus and abnormal urobilinogen changes were noted. Most of the findings in the cephalin flocculation test were in the zero to 1 plus range before we started. There was no ancillary evidence of hepatic toxicity at all. After discontinuation of medication the findings in all liver function studies returned to normal for both the carphenazine- and trifluoperazine-treated patients. All patients treated with trifluoperazine in doses of 20 mg. per day showed some degree of sedation. Even after reduction of the dose, six patients continued to show a disturbing lethargy.

REFERENCES

1. Niswander, G. D., and Karacan, I.: Prolixin in the Treatment of Mental Disease. *Clin. Review & Research Notes,* Vol. 2, Aug. 1959.
2. Taylor, I. J.: Clinical Experience with Prolixin. *Clin. Review & Research Notes,* Vol. 2, Aug. 1959.
3. Freyhan, F. A.: Extrapyramidal Symptoms and Other Side Effects, in Trifluoperazine, Clinical and Pharmacological Effects. Edited by H. Brill, Philadelphia. *Lea & Febiger,* 1958, p. 195.
4. Feldman, P. E.: Safety and Toxicity in Trifluoperazine, Clinical and Pharmacological Effects. Edited by H. Brill, Philadelphia. *Lea & Febiger,* 1958, p. 206.

Treatment of Chronic Schizophrenia with Parenteral and Oral Carphenazine

DOUGLAS GOLDMAN, M.D.*

Exploratory work with carphenazine was begun at Longview State Hospital in September 1959, and long-term investigation in December 1959 and January 1960. Treatment has been administered to more than 200 individuals over varying periods of time. This report describes the results and the side effects encountered with this group of patients.

At Longview the technic of therapy with any new drug is divided into several phases. The initial, exploratory phase consists of the treatment of a small pilot group, usually of not more than 10 or 12 patients. The agent under investigation must have been cleared for human administration by careful animal studies and adequate preliminary work with human volunteers. The patients receive the recommended dose, or less, at the start and the dose levels are increased to the point of therapeutic efficiency or production of side reactions. Observations of blood pressure and hematologic and chemical effects are made at regular intervals, not longer than weekly for the first month, and then every two to four weeks for three months or longer. For the initial studies, patients are chosen who have been treated with other drugs with little or no success. These are usually chronic psychotics, long time residents of the hospital. This puts the new drug to a severe test but it does not risk any patients who would be susceptible to improvement from drugs already available. Patients suffering from such chronic illnesses may not be considered particularly hopeful subjects for exploration of any new drug. However, we have found, in our experience of the past six years, in which more than 40 different new drugs have been used for treatment of more than 5000 patients, that every compound that has become a valuable addition to the psychiatric armamentarium has shown clear antipsychotic effect in several of the chronic patients in this exploratory group.

Drug therapy en masse in the manner we employ requires a carefully organized team of participants. This team consists of all the ward physicians in the hospital, under supervision of the clinical director and the senior physician of the staff, and a group of specially chosen registered nurses and psychiatric aides who assist the physicians in supervision of work with the individual patients, and keep regular card records of dosage, results and side effects. About 2200 inpatients and 750 outpatients are under such treatment in this institution. In the case of wards where the physicians tend to have inadequate interest, the drug team member serves as the extension of authority from the clinical director in conducting the drug project. No psychotherapeutic agent in the entire hospital is ordered except through the drug team; and no agent is discontinued, unless for emergency reasons, without approval from the drug team. This insures well-ordered studies.

Since more than two thirds of the patients in every ward and in the entire hospital are receiving or have received drugs of one kind or another, medica-

From the Longview State Hospital, Cincinnati, Ohio.

*Clinical Director, Longview State Hospital, Cincinnati, Ohio.

tion will be no unusual experience to any of them. In this way a group of patients has become available, over a period of years, in whom treatment with one or more drugs has produced little or no benefit. Such individuals are particularly useful subjects for further study of drug therapy since any useful effect will stand out against the previous background of failure. This represents an experimental pattern that is far superior to any double blind design, and produces more meaningful information on the therapeutic value of a drug, as well as knowledge of the side effects and toxicity that may be expected in clinical practice. This is not denying the value of double blind designs for specific purposes. However, for introduction of any drug into clinical practice, the technic described here is superior.

Since the psychotropic drugs have become clinically available, practically every patient admitted to state hospitals today has experienced drug therapy of some sort before. Schizophrenics usually have received electroshock and not less than two or three phenothiazine derivatives. It has been our general policy to discontinue when possible, all previous treatment for a sufficient length of time to determine the true status of the patient.

In our experience there are relatively few distinguishing characteristics among schizophrenic patients that would indicate one kind of drug therapy rather than another. It may be necessary to treat some with more intensely active compounds, even at the risk of neurologic side effects. Others may be more disturbed by the side effects than they are benefited by the same drugs. For such patients, drugs that have milder side reactions or none at all are more desirable. Intelligent patients report subjectively unpleasant effects from various phenothiazine compounds. In our experience there has been no consistency in the production of such reactions since some individuals may be tolerant to a drug or group of drugs that others find difficult to take, and the latter group may be able to benefit from drugs that the former find unpleasant. We cannot, therefore, say that we have used any special criteria for choice of patients except chronicity of symptoms.

As our experience matures our opinion undoubtedly will become more sharply determined in the choice of patients for individual drugs. At this time, the negative characteristics of certain agents are of more importance in some patients than the specific positive qualities. For instance, we have discontinued almost entirely the use of chlorpromazine because of its tendency to produce jaundice, occasional hypotension, and, rarely, agranulocytosis. We have used prochlorperazine, perphenazine and the newer, more intensely active, compounds such as trifluoperazine and fluphenazine more extensively.

Carphenazine represents a venture in the direction of compounds that produce less parkinsonism, or parkinsonism of milder degree. Presumably this agent will be more useful in older individuals who are more susceptible to unpleasant parkinsonian symptoms, and should be valuable because it produces less distortion of the results by neurologic side effects.

We found early in our experience that mentally disturbed patients are likely to be unreliable and not to be trusted in the taking of any medication. Their habits have not changed in the six years in which anti-psychotic and other agents have afforded more effective means of relieving psychotic symptoms. We,

therefore, believe firmly that any patient who shows little or no effect from a prescribed medication after a reasonable length of time is not taking the drug. Such an individual must be treated with oral liquid concentrates, the swallowing of which can be observed with more certainty than the ingestion of tablets or pills. When it is necessary to be absolutely certain that the dose is received, the parenteral route should be used. Patients who are initially resistant to treatment usually become sufficiently cooperative to swallow pills after an initial period of parenteral or oral liquid medication. An occasional chronically psychotic patient may require oral liquid medication for a long period.

Tables 1, 2, and 3 show the dosages of carphenazine we used initially for maintenance and for parenteral treatment. We generally find it most practical to divide the total daily dose into two equal portions administered twice a day. Occasional patients can get along with a single daily dose. The purpose of administering the drug is not to obtain the effect of single doses, but to build up a cumulative level in the nervous system that will control symptoms and help the patient to lead a more efficient life, undisturbed by psychotic functioning. Most patients on maintenance therapy receive 50 to 200 mg. daily. This probably represents a conservative dosage; over an extended period of time increase of the dose may be required.

At this dose level, carphenazine has been singularly free from evidences of real toxicity. Table 4 shows the side reactions we have encountered. The parkinsonism and related phenomena produced by carphenazine were looked for more intensively and observed more critically, perhaps because of the relative mildness of such side effects, than had been done in studies of other drugs more active in production of such disturbances. Even at high dose levels and for long periods of time, less than 10 per cent of the patients receiving carphenazine required anti-Parkinson medication to enable continuance of treatment. Somnolence occurred in a significant proportion of individuals, after medication by the oral as well as the parenteral route, particularly early in treatment.

In common with other effective anti-

TABLE 1

Initial Oral Dose of Carphenazine

Mg./Day	No.	Most Commonly Used Doses Mg./Day	No.
25	32		
26- 50	111	25	37
51- 75	24	50	104
76-100	53	100	53
101-300	8		
Total	228	Total	194

TABLE 2

Maintenance Oral Dose of Carphenazine

Mg./Day	No.	Most Commonly Used Doses Mg./Day	No.
25	10	25	10
26- 50	78	50	75
51-100	37	100	34
101-200	25	200	20
201-300	14	300	13
301-900	6		
Total	170	Total	152

TABLE 3

Intramuscular Dose

	Mg./Day	Most Commonly Used Doses Mg./Dose
Minimum	7.5	15.0
Maximum	200.0	100.0
Average	60.0	30.0

psychotic drugs, carphenazine produced, in an appreciable number of individuals, the subjective disturbance now spoken of as "turbulence." This was first observed during reserpine treatment by Barsa and Kline, and subsequently was reported by many others, including the present author, during use of certain active phenothiazine derivatives. No jaundice or hematologic abnormality has occurred from carphenazine, and thus far, even with the higher doses, no allergic manifestations such as dermatitis or urticaria. One patient experienced mild lowering of the blood pressure, which was not necessarily attributable to the compound, and one patient was slightly nauseated.

Intramuscular administration of carphenazine (Table 5) produced side effects approximately similar to those observed from oral medication. Again, parkinsonism developed in a smaller percentage of patients than had occurred during treatment with other potent antipsychotic agents. Somnolence was produced somewhat more readily than with carphenazine by the oral route but the difference was slight. Local irritation from the injection was seen in less than 10 per cent of the individuals.

The time of onset and the dosage at which parkinsonian symptoms developed are shown in Table 6. Onset apparently occurred first, in susceptible patients, within the first week of treatment; and second, in other patients only after thorough saturation with the drug over, perhaps, three weeks or more of medication, sometimes after two months or longer. The parkinsonism that occurred early was often transient and, unless the dystonic reactions were of greater than usual intensity, did not require anti-Parkinson treatment. Parkinsonism that developed later often required anti-Parkinson drugs. Most patients who experienced parkinsonian symptoms had received more than 50 mg. daily. The parkinsonism that may develop during medication with this as well as other phenothiazine derivatives is in our experience to be considered simply an index of saturation with the drug and is certainly not a necessary feature of successful pharmacologic therapy.

The akathisia and dystonic reactions produced by carphenazine are recognizable but usually less intense than those observed during treatment with other piperazine derivatives (prochlorperazine, fluphenazine and similar compounds). The occasional, more severe, dystonic reactions respond readily to anti-Parkinson agents (Cogentin®, Akineton®, Disipal®, and the like) injected intravenously.

TABLE 4

Side Effects

Carphenazine Administered Orally to 228 Patients

		Received Anti-Parkinson Drug
Parkinsonism	33	15
Akathisia	7	1
Dystonia	6	2
	46	
Somnolence	37	(16.2%)
Turbulence	8	
Nausea	1	
Lowered Blood Pressure (Mild)	1	

TABLE 5

Side Effects

Carphenazine Administered I.M. to 57 Patients

Parkinsonism	5
Dystonia	2
Somnolence	11
Sore Buttocks	5

TABLE 6

Details of Parkinsonism in Carphenazine-Treated Patients

	Days	Males	Females
Time of Onset:	1-10	1	8
	11-20	0	3
	21-30	2	6
	31-50	2	4
	50 —	4	3
	Total	9 (of 93 pts.)	24 (of 135 pts.)

	Mg./Day	No. Pts.	Males	Females
Dose at Onset:	50	6	1	5
	51-100	15	4	11
	101-300	10	3	7
	Over 300	2	1	1
	Total	33	9	24

The results of treatment were graded as follows:

A. Patients had recovered from all active psychotic manifestations, particularly had lost all delusions and hallucinations, had acquired insight into previous delusions and hallucinations; showed adequate affect, and social and industrial adaptive capacity equal at least to that of the premorbid condition; and exhibited no overt hostility, particularly to the hospital or its staff.

B. Individuals had recovered from most psychotic manifestations, but might not have lost belief in previously present delusional experience, and were able to make a satisfactory social and industrial adaptation away from the hospital, or in the hospital under privileged conditions. The improvement of these patients may be summarized as "a good social remission."

C. Patients had improved, in comparison with the initial condition, in significant ways, particularly in ability to communicate verbally, in elimination or diminution of assaultiveness, incontinence, denudativeness, and other gross manifestations of psychosis; and in some diminution but not actual resolution of psychopathologic manifestations, such as delusions and hallucinations.

D. Patients had improved only slightly or not at all.

E. Patients had become more psychotic (schizophrenic or manic).

The results of treatment are shown in Tables 7, 8, 9 and 10. Gross results are shown in Tables 7 and 8. Table 7 shows the results obtained in patients who had been treated for three months or more with carphenazine. In our experience, at least three months are required to produce therapeutic benefit in significant numbers of psychotic patients with any medication and much longer therapy may be required in some cases. These figures are, therefore, to be considered as extremely conservative in expressing the effectiveness of the antipsychotic activity of this material. Table 8 shows some of the earlier results in 82 patients who have to the present time received treatment for one to three months. Even in this group, some of the more chronic patients are beginning to show clear evidence of remission.

Table 9 shows progressive improvement in an increasing proportion of the group as the time of treatment is extended. The compound has not been in use long enough to supply closed group tables for a period of a year or more, such as we have published on other substances, but the results in a group of 28 patients under treatment for six months or more are shown in Table 9. It is fully expected that improvement will occur in additional members of the

TABLE 7

Results of Treatment for Three Months or More

ALL DIAGNOSES	GRADE				SCHIZOPHRENIA	GRADE			
Time in Hospital	A	B	C	D	*Time in Hospital*	A	B	C	D
<6 months	3	17	32	2	<6 months	2	11	24	2
6 months–2 years	–	3	11	4	6 months–2 years	–	2	7	1
2 years–5 years	–	–	15	7	2 years–5 years	–	–	6	4
>5 years	–	1	37	9	>5 years	–	–	28	6
Total—141 patients					Total—93 patients				

TABLE 8

Results of Treatment for One to Three Months

ALL DIAGNOSES	GRADE				SCHIZOPHRENIA	GRADE			
Time in Hospital	A	B	C	D	*Time in Hospital*	A	B	C	D
<6 months	–	1	18	9	<6 months	–	–	16	8
6 months–2 years	–	1	9	5	6 months–2 years	–	–	4	3
2 years–5 years	–	1	8	–	2 years–5 years	–	1	4	–
>5 years	–	1	10	5	>5 years	–	–	8	3
Total—68 patients					Total—47 patients				

group as the dosage level is raised and time of treatment prolonged.

Table 10 shows chiefly that there are only a few previously untreated schizophrenics available in state hospitals. A significant proportion of such individuals in this institution obtained satisfactory benefit from treatment with carphenazine for three months or more, and those who had been previously treated with other agents also showed adequate benefit from carphenazine.

Other data showed that carphenazine is capable of producing improvement after other drugs had failed or had evoked only transient effects (table 11). Most of these patients had achieved satisfactory recovery on treatment with other drugs and then had relapsed after stopping maintenance medication with the original agent. Thus far, we have been able to bring back a significant proportion of such individuals to a satisfactory level of functioning with carphenazine and have not had an undue number of failures considering the extremely resistant nature of the illness in these patients.

TABLE 9

Results of Continued Treatment in 28 Patients

	GRADE			
	A	B	C	D
3 months' treatment	2	5	20	1
6 months' treatment	2	8	17	1

The results show that carphenazine, in its ability to relieve psychotic manifestations, is comparable to the other useful antipsychotic substances presently available. It is naturally difficult to make an adequate comparison with drugs that have been in use for two to four years or more. The early records on chlorpromazine and trifluprom azine show data quite similar to that shown here for carphenazine, with the reservation that the data on carphenazine have been judged with more severity as well as sophistication than was the earlier material. With further experience it may be found that the antipsy-

TABLE 10

Results of Treatment of Schizophrenia for Three months or More

Previously Untreated (16)					Previously Treated (77)				
	Grade					Grade			
Time in Hospital	A	B	C	D	*Time in Hospital*	A	B	C	D
<6 months	1	2	12	1	<6 months	1	9	12	1
6 months–2 years	–	–	–	–	6 months–2 years	–	2	7	1
2 years–5 years	–	–	–	–	2 years–5 years	–	–	6	4
>5 years	–	–	–	–	>5 years	–	–	28	6

chotic effect of carphenazine is equal to that of other piperazine derivatives, such as prochlorperazine and perphenazine. At this time it appears that the trifluoromethyl piperazine derivatives, such as trifluoperazine and fluphenazine, have greater antipsychotic effect. Carphenazine, however, has the distinct advantage of being less productive of parkinsonism and therefore interferes less with the ordinary functions of everyday life.

In summary, carphenazine is effective for treatment of psychotic manifestations in schizophrenia, is free from serious side effects, has less tendency to produce parkinsonism than other active phenothiazine derivatives, and the parkinsonism associated with carphenazine medication is milder and more readily controllable than is the parkinsonism produced by other active phenothiazine compounds. These factors, in our opinion, should give carphenazine a place of usefulness in the therapeutic armamentarium against psychotic illness.

TABLE 11

Results After Previous Phenothiazine Treatment

*(153 Pts.)**

	A & B	Failures (D)
Other phenothiazine (previously)	36	29
Carphenazine	14	36

**Note*: Patients in this group represented eventual failures, chiefly for lack of follow-up treatment, even after original "A" or "B" result.

DISCUSSION

Dr. Page: What was the basic activity pattern of this patient population? Were they underactive or overactive patients when you employed this treatment?

Dr. Goldman: Chronic patients go through phases of both. The patient who has been sitting quietly in the ward for several weeks may suddenly get up and break 20 panes of glass. Grossly psychotic individuals who have been in the state hospital a long time may become overactive. They lose their psychotic uniformity and reach a rather normal diversity of behavior as a result of treatment.

Dr. Page: How old is the oldest patient you treated with this drug?

Dr. Goldman: In the 70's.

Dr. Page: Do you find that the drug tolerance is better in the older age groups?

Dr. Goldman: There is no difference.

Dr. Merlis: I was impressed with the statistics on the large number of apparently chronic patients who did so well. Were they discharged to their homes?

Dr. Goldman: Yes. Fourteen improved of 153 patients previously treated with other phenothiazine compounds, who had not responded or who had relapsed. This represents about 9 per cent improvement. This is a rather good percentage for such a chronically resistant group.

Dr. Page: Your data point out a very important fact in relation to the chronic psychotic—that unless you treat these patients for more than three months you will not begin to see a real therapeutic response. This highlights a problem often encountered in designing control studies. Blind cross-over or blind noncross-over studies are usually conducted for a limited period of time, which may be insufficient to obtain optimal therapeutic effects.

Dr. Goldman: I wish to say also that this drug functions well in the control of manic reactions and relieves delirium tremens.

Carphenazine Therapy in Hospitalized Patients

NAUTTAM J. KOTHARI, M.D., IN HO PARK, M.D., NATHAN S. KLINE, M.D., and JOHN C. SAUNDERS, M.D.

Carphenazine was evaluated in hospitalized psychotic patients to determine the clinical efficacy of the compound and to see if it had clinical properties significantly different from those of other available phrenotropic drugs. Studies in the past revealed that the phenothiazine derivatives have three fundamental clinical actions: antipsychotic, sedative and extrapyramidal. The ideal phrenotropic drug would alleviate both the primary and secondary symptoms of schizophrenia as described by Bleuler, and be free of sedation and extrapyramidal reactivity. To date such a preparation remains theoretical. However, carphenazine appears to provide a useful balance between the relief of psychotic symptoms and untoward reactions; and in addition, possesses the property of ameliorating the primary symptoms in a significant number of patients. The lack of such function has limited the usefulness of the phenothiazine derivatives in psychopharmacology; the psychic energizers, alone or in combination with a tranquilizer, have been required.[1]

Selection of Patients

This study included two groups of patients. One group consisted of 25 male schizophrenics hospitalized from three to nineteen years, with an average of ten years. In this group were 12 patients with dominant symptoms of autism, detachment from reality, disturbance of affectivity, associational deprivation and secondary symptoms of delusions, hallucinations and dereistic behavior. The remaining 13 patients in the group were characterized by a reversal of the primary and secondary symptoms. These patients were part of a comparative study with other phrenotropic agents.[2] The second group included 23 male schizophrenics who had been hospitalized from two to twenty-one years. Their symptoms were about equally distributed between the primary and secondary; catatonic excitement was the dominant psychic pattern in 1 patient; depression with flat affect, in 8; autism, in 1.

The patients received carphenazine in doses ranging from 50 to 600 mg. orally per day. The majority received a total daily dose of 150 to 300 mg. administered in divided doses three times a day, as this schedule provided the optimum therapeutic effect. Thirteen patients received carphenazine for a minimum of two to a maximum of eight months. Adjunctive therapy was not given; the dosage was adjusted to obtain the desired clinical response. Maintenance therapy was usually administered in doses of 50 mg. three times daily.

RESULTS

The results of carphenazine therapy in these chronic schizophrenics are presented in Table I. Many chronic, severely psychotic patients responded to carphenazine in twelve weeks. Experience with chlorpromazine and older phenothiazine compounds initially led to the conclusion that a minimum of six months was required for adequate trial. Carphenazine, like trifluoperazine and perphenazine, is capable of producing a therapeutic effect in a three month period. With trifluoperazine irritability is relatively frequent,[3] and motor retardation is elicited by perphenazine in a significant number of patients.

From Research Facility, Rockland State Hospital, Orangeburg, N. Y.

TABLE 1

Results of Carphenazine Therapy

	SYMPTOMS		
	Primary	Secondary	Total
Worse	2	2	4
No Change	12	9	21
Improvement			
Slight	3	4	7
Moderate	3	5	8
Pronounced	3	5	8
	23	25	48

Most of the patients in this series had failed to respond to previous phrenotropic therapy. Approximately 5 per cent could be expected, from the experience in previous studies, to show significant response on repetition of the treatment. We, however, obtained an 8 per cent discharge rate in these patients who had been previously treated; therefore, this preparation produced better results than might have been expected from readministering the initial drug.

Of the 23 patients who responded to carphenazine there were 9 whose primary as well as secondary symptoms significantly improved. We believe this property adds considerably to the usefulness of carphenazine, as it is essential that both groups of symptoms be controlled before discharge.

We have been asked about the criteria for discharge: It is our opinion that a patient must be able to get along with himself and his associates if he is to remain outside the hospital and to fulfill his duties in the community. This means that subsidence of disorders in thought and affect, accompanied by integration of personality, must be achieved before release; this signifies pronounced improvement. Moderate improvement is interpreted as a reduction of hypermotility of thought and behavior. Slight improvement is the result merely of the drug's sedative action.

Side Actions

The side actions of carphenazine usually appeared at dose levels of 100 mg. daily and above. Liver dysfunction and blood dyscrasias were not observed during the study. Five patients became drowsy, four exhibited akathisia, rigidity developed in five, and tremor in one. One complained of muscle pain in the right shoulder. One died after eight weeks of therapy at 50 mg. daily; the autopsy disclosed generalized arteriosclerosis and ischemic heart disease without histopathological evidence of untoward reaction to the medication.

CONCLUSIONS

These results indicate that the therapeutic efficacy of carphenazine in chronic schizophrenic patients is comparable to that of the presently available phrenotropic drugs, and that the compound may alleviate some of the primary symptoms of schizophrenia. Phenothiazine agents with a high sedative activity are of little benefit in the withdrawn schizophrenic, and phenothiazine compounds with low sedative action frequently produce a high level of irritability, hostility and even aggression after three months of therapy. Carphenazine may be characterized as a useful antipsychotic agent for the withdrawn schizophrenic. Sedation and extrapyramidal reactivity are mild and infrequent.

BIBLIOGRAPHY

1. Gosline, E., Bluestone, H., and Saunders, J. C.: Beta-phenylisopropylhydrazine and Its Use in Psychoses. *J. Clin. & Exper. Psychopath.*, 21: 220, 1960.
2. Kothari, N. J., Saunders, J. C., Kline, N. S., and Griffen, J. A.: A Comparison of Perphenazine, Proketazine, Nialamide and MO-482 in Chronic Schizophrenia. *Am. J. Psychiat.*, 117: 358, 1960.
3. Barsa, J. A., and Saunders, J. C.: Trifluoperazine Combined with Chlorpromazine. *Am. J. Psychiat.*, 116: 925, 1960.

Clinical Evaluation of Carphenazine

D. W. McCreight, M.D.*

Purpose of Study

The purpose of this study was to determine the therapeutic effectiveness of carphenazine, a piperazinyl derivative of phenothiazine, recently introduced for the psychopharmacologic treatment of chronic, withdrawn, schizophrenic patients.

Method of Study

The series included 47 patients, 23 males and 24 females, with a clearly established diagnosis of schizophrenia, and ranging in age from 24 to 68 years. Chronicity, in terms of hospital residence, ranged from two to 38 years. This biased sample was divided into:

Subgroup 1, 15 patients (7 males and 8 females) who were mildly withdrawn. (The eighth male in this group had been dropped at the beginning of the study because of persistent weight loss during the baseline evaluation.)

Subgroup 2, 16 patients (8 males and 8 females) with moderately withdrawn behavior.

Subgroup 3, 16 patients (8 males and 8 females) in whom withdrawal was severe.

The design of the investigation included five phases: Phase I, baseline studies; Phase II, comparison of placebo and active treatment groups; Phase III, active treatment of all patients; Phase IV, reinstitution of a comparison of active treatment and placebo groups; Phase V, post-treatment evaluation.

Phase I. Medication was withdrawn from all groups for one month. An initial baseline rating was then made, and the studies were continued over a period of two months, during which time the patients were still without medication. A second baseline rating was made at the end of Phase I.

The studies included observations by psychiatrists, nurses and psychiatric technicians; laboratory determinations supplemented the psychiatric, physical and neurological evaluations. The Wittenborn Psychiatric Rating Scale, the Wittenborn Supplement for Chronic Schizophrenic Patients, the Standard Mental Status and standard progress notes also were completed. The nurses were responsible for physiological studies, such as temperature, pulse and respiration; blood pressure, weight, appetite; and of sleep and bowel habits. The nurses and psychiatric technicians made the observations for the Burdock Ward Behavior Rating Scale. At each evaluation period two sets of these ratings were made independently, by a nurse and a technician, for each patient.

Phase II. At the start of the treatment period, one half of the patients in each subgroup (designated as Group A) were given the active compound carphenazine; and one half (designated as Group B) received the identical-appearing placebo, administered by double blind procedure. Thus 50 per cent of each subgroup received the active compound. The dosage schedule for the first week was 20 mg. twice a day; for the second week, 20 mg. three times a day. This was increased to 40 mg. three times a day for the remaining six weeks of this eight week treatment period. All baseline studies were then repeated.

From Marlboro State Hospital, Marlboro, N. J.
*Assistant Medical Director, Marlboro State Hospital, Marlboro, N. J.

Phase III. All patients received the active compound for 16 weeks. During this phase the dosage schedule was gradually increased to a maximum of 80 mg. three times a day for two weeks, or a total dose of 240 mg. daily; then was reduced for two weeks to 60 mg. three times a day; and for the remainder of the period a dosage of 50 mg. three times a day was maintained. During active treatment of all patients, the total daily dosage varied from 120 mg. to 240 mg. with the entire group maintained during the final four weeks of Phase III on a total daily dosage of 150 mg. At the end of this period all baseline studies were repeated.

Phase IV. The original active treatment and placebo groups were reinstituted on a fixed treatment schedule of 50 mg. twice a day for Group A. At the conclusion of this phase, all baseline studies were repeated.

At the conclusion of Phase IV, Group A had been under continuous active treatment from September 9, 1959 until April 8, 1960, or approximately seven months. Group B had been on placebo treatment for eight weeks, on drug treatment for sixteen weeks, and on placebo treatment for the final four weeks.

Side Effects

Extrapyramidal symptoms — mainly rigidity of extremities, masked facies, slow deliberate gait, retardation of verbal responses and increase in salivation —were the most noticeable side reactions. These symptoms were observed in 10 of the 16 female patients in the mild and moderate groups (Subgroups 1 and 2) during the period when all patients were receiving medication.

One Group A male patient, in the subgroup classified as mildly withdrawn, developed oculogyric crises during the initial medication period. These were controlled by Akineton. Medication was discontinued for this patient for two days prior to Phase IV. After his second dose of 50 mg. of the compound oculogyric crises developed again. This, I believe can be attributed to an individual idiosyncrasy to the substance.

One Group B female patient, in the subgroup classified as moderately withdrawn, had a reactivation of an acute catatonic stupor, which required forced feeding. The reaction set in after Phase III, when all patients had been receiving medication, and was so severe that she remained in a kneeling, prayerful position most of the time, so that it was necessary to remove her from the project.

In the severely withdrawn and older patients (Subgroup 3) one Group A and two Group B female patients died from severe respiratory infection during an influenza epidemic. One Group B female patient, who had a kyphoscoliosis and who was diagnosed as mildly withdrawn, died during the same epidemic. Postmortem examination showed that this patient also had had a very poorly developed cardiovascular system. Another had been luetic.

RESULTS

Physiological. Review of blood morphology indicated no significant change in the white blood count in either group A or B. Four female patients in Group A and one female in Group B showed a slight decrease in the erythrocyte count. In no instance did the decrease exceed 800,000 red blood cells.

Metabolic and Biochemical. There were no significant changes in blood pressure, sleep pattern, appetite or bowel habits in any of the patients. Liver studies showed no essential changes.

The average weight loss for the 12

males in Group A, who received the active compound, was 16 pounds. The average weight gain for this group was 10 pounds. In the 12 females in the same group the average weight loss was six pounds.

In Group B, who received the placebo, the data for Phase II do not show any significant change in weight. However, the over-all rating for this group includes a period of medication with the drug, or Phase III. The terminal average weight loss for the 11 males in this group was nine pounds; the average weight gain, 10 pounds. For the females in the same group, the average weight loss was five pounds and the average weight gain, 26 pounds. This evidence is suggestive, but not conclusive, of an appetite-suppressant effect of the drug.

Neurological. The only neurological findings were extrapyramidal symptoms. These are reported under side effects.

Behavioral Evaluation

1. *Burdock Ward Behavior Rating Scale.* The Burdock Ward Behavior Rating Scale provides a measure of severity of illness and an index of response to treatment for mental patients. The Scale consists of 150 items drawn from three categories of observation. These categories are appearance and deportment, behavior in verbal context, and adaptation to ward routine. The items were constructed so as to reflect observable units of behavior. They describe such activities as facial expression and grooming, eating and toilet habits, physical status, attitudes, cooperativeness, communicability, vocalization and speech patterns, interpersonal relations, hostility or aggressiveness, mannerisms, affect and special symptoms.

Two baseline Ward Behavior Rating Scales were completed, making a total of five such ratings. At each of the five periods two ratings were received for each patient, from two different observers. Ratings for the male patients averaged 90 per cent reliability and for the female patients they averaged 65 per cent reliability.

Among the males, there was a significant rise in the mean scores for Group A from the first to the final rating. Group B showed a similar significant rise in the mean scores from the second rating period (end of placebo treatment) to the fourth rating period (end of drug treatment). Among the females, the difference between these rating periods was not significant. However, over the various periods a slight trend to increased mean scores was apparent among the Group A subjects, whereas the mean scores for Group B fluctuated, showing no consistent trend.

Fig. 1, entitled "Mean Scores on Ward Behavior Rating Scale," indicates the improvement in the A or treatment group for both male and female patients. Clearly there is a significant rise in the mean score for the males in this group; for the females in the same group, there is a rise, but not as significant a one, in the mean score.

During the third rating period, when all patients were on the medication, there was a noticeable although slight improvement in the mean scores of both groups.

2. *Clinical Evaluation by Physicians and Nurses.* Clinical evaluations were made at the end of Phase III, during which all patients received the active compound, and at the end of the study. At the end of Phase III one of the female patients in Group A was rated as being much improved; three were slightly improved, seven were un-

FIG. 1 Mean Scores of Ward Behavior Rating Scales for Study of Carphenazine

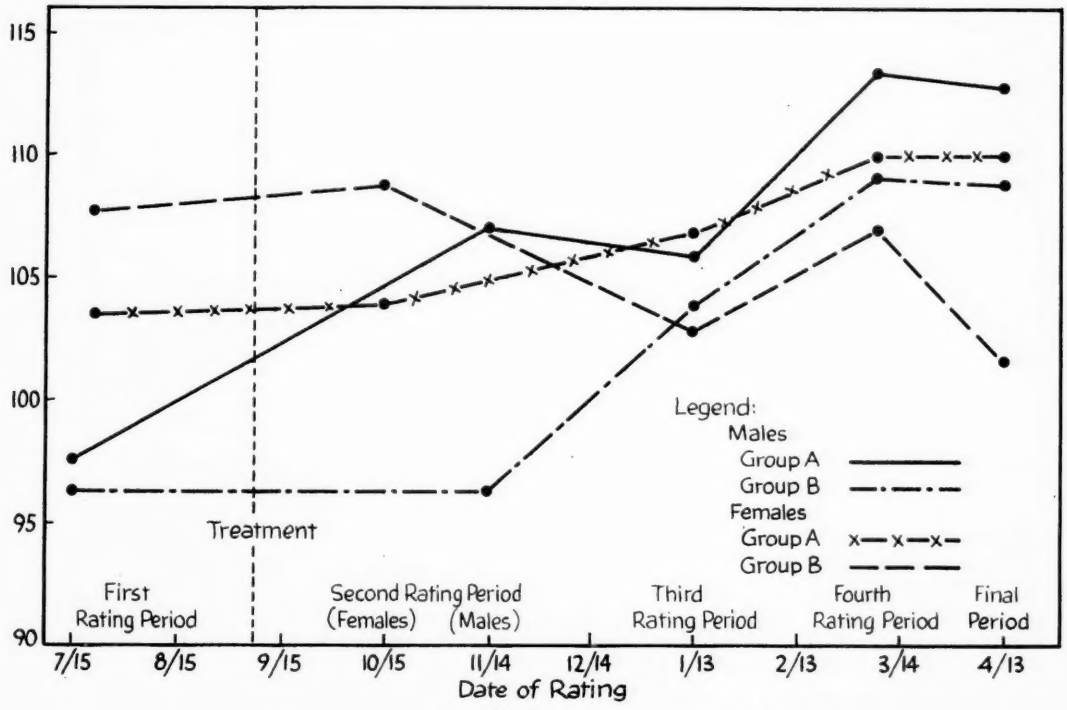


Figure 1.

changed, and one was worse. Of the Group A males two were rated as being much improved at the end of Phase III, eight as slightly improved and one as worse.

In Group B, at the end of Phase III, one female patient was rated as much improved, four as slightly improved, six as unchanged and one as worse. Of the male patients in Group B, two were rated as being slightly improved, nine as unchanged, and one as worse.

Table 1 shows the physicians' and nurses' clinical evaluations of the patients' responses at the end of the study.

In summary, in the treatment group, including both males and females, one patient was considered to have become much improved and two slightly improved; 16 patients showed no change, three were worse, and one expired.

In Group B, who received the placebo, four patients were rated as slightly improved, 10 showed no change, seven were worse, and three expired.

All deaths occurred from influenza.

Psychiatric Evaluation

1. *The Wittenborn Psychiatric Rating Scale* and the Wittenborn Supplement for Chronic Schizophrenic Patients showed no significant improvement or deterioration in the baseline and final evaluations for either Group A (treated patients) or Group B (placebo).

2. *The Standard Mental Status.* The Chronic Schizophrenic Profile consists of a checklist of items arranged in categories, as personal appearance, observable behavior, emotional behavior or affective processes, speech and intellection or thought processes. Of the

TABLE 1

Clinical Evaluations by Physicians and Nurses at Termination of Study

GROUP A	Diagnosis	M.D. Rating	R.N. Rating	GROUP B	Diagnosis	M.D. Rating	R.N. Rating
Mild, F	2 Hebephrenic	NC	NC	Mild, F	2 Paranoid	W	W
	1 Catatonic	W	W		1 Paranoid	Exp.	Exp.
	1 Catatonic	SI	SI		1 Hebephrenic	SI	SI
Moderate, F	3 Paranoid	NC	NC	Moderate, F	2 Catatonic	W	W
	1 Paranoid	SI	SI		1 Hebephrenic	W	W
					1 Paranoid	NC	SI
Severe, F	1 Catatonic	W	W	Severe, F	1 Catatonic	W	W
	1 Hebephrenic	NC	NC		1 Hebephrenic	Exp.	Exp.
	1 Hebephrenic	W	W		1 Paranoid	Exp.	Exp.
	1 Paranoid	Exp.	Exp.		1 Paranoid	W	W
Mild, M	2 Hebephrenic	NC	NC	Mild, M	1 Catatonic	NC	NC
	1 Hebephrenic	MI	MI		2 Hebephrenic	NC	NC
					1 Dementia Praecox	NC	NC
Moderate, M	2 Catatonic	NC	NC	Moderate, M	1 Paranoid	NC	NC
	1 Dementia Praecox	NC	NC		1 Paranoid	SI	SI
	1 Hebephrenic	NC	NC		1 Catatonic	SI	SI
					1 Dementia Praecox	NC	NC
Severe, M	2 Hebephrenic	NC	NC	Severe, M	4 Hebephrenic	NC	NC
	1 Paranoid	NC	NC				
	1 Dementia Praecox	NC	NC				

MI—Much Improved
SI—Slightly Improved
NC—No Change
W—Worse
Exp.—Expired

115 items included in this form, the responses to four were found to have statistical significance when the patients' profiles were compared in the baseline and final evaluations.

In an item rating ability to obtain and maintain attention, significant improvement was found in five patients (4 females and 1 male) in Group A.

In an item evaluating inappropriate affective responses, a significant improvement was found in nine patients (6 females, 3 males) in Group A. The more frequent improvement among the females may be partially explained by the high incidence of extrapyramidal symptoms among the female patients.

In an item evaluating vagueness of verbal response, a significant increase was noted in both Group A and Group B. Twenty-four patients, 13 in the placebo and 11 in the treatment group, showed increase of this symptom.

3. *Scales for Chronic Patients* consist of 20 categories designed to measure changes in symptomatic behavior. In each category ratings were made on a continuum ranging from A to D in the direction of the most extreme manifestation of behavioral disorder. The patients' baseline and final evaluations were compared.

Statistical analysis indicated significant improvement in three of the 20 categories for Group A. In an item measuring expression of hope for and interest in recovery, improvement was significant at the .05 level. In an item concerned with the use of hospital facilities, the change was significant at the .01 level. Finally, in an item measuring the appropriateness of smiling and laughter, improvement was found to be significant at the .05 level.

In the B Group, improvement was statistically significant in two of the 20 items. In an item evaluating orientation, a change in the direction of greater orientation was found to be significant at the .05 level. In an item evaluating the severity of facial tics and grimaces, improvement was significant at the .05 level.

DISCUSSION

The overall results of the first study did not indicate that carphenazine was significantly effective in the treatment of chronic schizophrenic patients who exhibited withdrawn behavior of varying degree. At the end of Phase II, when one half of the total series had been receiving drug and one half had been receiving placebo, there was a slight but not significant difference in the response of the two groups. There was more mobility in the medicated group as compared to the placebo group. However, at the end of Phase III, after both groups had been receiving medication, this difference was negligible. At the conclusion of the study, when Groups A and B had been reinstituted, no statistically significant improvement could be demonstrated.

Changes in the profile of the individual patient did suggest improvement for some in certain particular reactions, such as affect, social participation and sensorium. Not all of the changes could be related to over-all improvement, as in ward behavior. Nevertheless, continued clinical evaluation on a broader symptom profile appeared to be justified. We therefore extended our treatment series to include an uncontrolled clinical trial.

The sample comprised 84 male and female patients, essentially unrestricted in terms of age, sex, diagnosis or duration of illness. A simple standard rating form was used. Reporting psychiatrists and ward personnel collaborated in filling out the forms, which rated

the intensity of no more than five symptoms on a scale ranging from 0 to 4. The data were collected and analyzed to determine whether the patient was *much improved, improved, unchanged* or *worse.*

The criterion for *much improvement* was significant change in three or more symptoms; for *improvement,* demonstrable change in at least two symptoms.

The period of treatment ranged from one to 37 days. Most patients were treated for approximately two weeks with dosages that averaged 60 mg. twice a day.

Three treatment areas were selected: female reception ward, women's continuous treatment service, and male senile infirmary service. In the female reception service a total of nine patients were treated, ranging in age from 20 to 44 years, median 34 years. Diagnostic categories included manic-depression, manic type, 2; schizophrenia, 2; psychoneurosis with anxiety reactions, 3; alcoholic addiction, 1; mental deficiency with psychotic reaction, 1. These patients were all new admissions, although some had had psychotic episodes previously. Of these nine patients, three were considered much improved, two improved, three unchanged, and one worse.

A total of 63 patients, ranging in age from 19 to 83 years, median 43 years, were treated on the women's continuous treatment service. Duration of illness ranged from eleven months to forty-six years, median eight years. Diagnostic categories included schizophrenic reactions, 41; mental deficiency with psychotic reaction, 6; manic-depression, manic type, 4; manic depression, depressive type, 2; chronic brain syndrome (CAS—chronic arteriosclerotic brain disease), 5; chronic brain syndrome with senile brain disease, 3; chronic brain syndrome with convulsive disorder, 1; and involutional psychosis, paranoid type, 1.

Of the 63 female patients in this group, five were much improved, 31 improved, 22 unchanged and five worse.

In the Men's Senile Infirmary, a total of 12 patients were treated. Ages ranged from 25 to 63 years, median 50 years. Duration of illness ranged from three months to 30 years, median duration seven years. Diagnostic categories included schizophrenic reactions, 7; manic depression, manic type, 1; mental deficiency with psychotic reactions, 2; chronic brain syndrome, senile brain disorder, 1; and chronic brain syndrome, convulsive disorder, 1.

Of the 12 male patients three were improved, eight were unchanged, and one became worse.

Table 2 shows the diagnostic groups and the ratings for this additional experimental group. Converting the figures into percentages, we find that 52 per cent of the population showed some improvement, 39 per cent were unchanged and 9 per cent were considered worse.

Analysis of the response in symptom groups discloses the following changes: Of the 72 female patients, 29 had exhibited behavioral changes characterized by withdrawal, seclusiveness, resistiveness, and negativism. Eighteen of these (62 per cent) achieved some degree of improvement. Nine had exhibited some form of aggressive behavior including assaultiveness and destructiveness; of these seven (78 per cent) were somewhat improved.

In the area of motor activity, 31 patients had presented a pattern of overactivity. Twenty-one (67 per cent) achieved some degree of improvement.

TABLE 2

*Diagnosis and Ratings for Experimental Group**

Diagnosis	Number of Patients	Much Improved	Improved	No Change	Worse
Schizophrenia	50	4	24	19	3
Manic Depressive, Manic Type	6	2	2	1	1
Manic Depressive, Depressive Type	2	0	1	1	0
Mental Deficiency with Psychotic Reaction	9	1	2	4	2
CBS. CAS	5	1	3	1	0
CBS. Senile Brain Disorder	4	0	1	3	0
CBS. Convulsive Disorder	3	0	2	1	0
Psychoneurosis, Anxiety Reaction	3	0	0	2	1
Alcoholic Addiction	1	0	0	1	0
Involutional Psychosis, Paranoid Type	1	0	1	0	0
Totals	84	8	36	33	7

*No significant differences existed in median age and median duration of illness among the various diagnostic groups or categories of improvement, or between male and female patients.

Five patients had exhibited evident motor retardation. Of these none improved. Sixteen patients had been talkative. Twelve of these (75 per cent) showed improvement. In the area of speech nine patients had been unproductive; three of these showed improvement.

Affective symptoms included anxiety, hostility, depression and euphoria. Four patients had presented clearly evident anxiety, of whom one showed improvement. Seven patients had exhibited marked hostility, of whom five improved. Fourteen patients had been depressed; eight (57 per cent) of these improved. Four patients had exhibited typical euphoria; one improved.

Tension was evident in 22 patients at start of medication. Eight (36 per cent) became more relaxed. Disorders of thought content included delusions of persecutory, grandiose, nihilistic and somatic types. Sixteen patients had presented one or more of these symptoms; seven (44 per cent) improved. Disorders of perception in the form of hallucinations occurred in 14 patients. Nine (64 per cent) showed improvement. Clouding of sensorium in the form of confusion had been present in five patients; four improved.

Side Effects

Five of the total group exhibited increased agitation. This was the only symptom that appeared to have worsened in more than one patient.

Ten patients exhibited a total of seven side effects. Six exhibited drowsiness, two dizziness, two tremor, two parkinsonian syndrome, one intense salivation, one profuse diaphoresis and one akathisia. Multiple side effects occurred in five of these patients.

DISCUSSION

The results of the extended clinical trial are suggestive of therapeutic activity. In the uncontrolled study, improvement was not statistically greater than would have occurred by chance. However, the improvement in the symptom profile, particularly in the chronically ill patients, did indicate pharmacological activity. Reduction of motor and of psychomotor overactivity, particularly in speech, resembled that from

other phenothiazine compounds. Patients in whom motor retardation was present showed less improvement. Affective symptoms, such as depression and hostility, also showed improvement. Changes in thought content and perception were less evident. Contrasting the results in the initial study, however, there was a trend toward a more appropriate behavioral response in the areas of both social withdrawal and aggressiveness.

The incidence of extrapyramidal symptoms and drowsiness was similar to that from other phenothiazine derivatives.

Obviously the results obtained in the initial and extended studies cannot be directly compared. Patient selectivity, duration of treatment, possible differences in the solubility of the compound, sensitivity of rating devices and the over-all rigidity of criteria for improvement undoubtedly play a role. Although pronounced spontaneous changes in the patients would not have been expected, in the first study, experience has shown that individual and possibly intrinsic fluctuations are seen in behavioral patterns of chronic schizophrenics if they are observed over a prolonged period.

SUMMARY

Of the first series, a controlled study comprising 23 chronic schizophrenic patients who received carphenazine for seven months, three were improved, 16 were unchanged, three became worse and one expired. In the control group of 24 patients who initially received placebo, carphenazine, then placebo, four were improved, 10 were unchanged, seven became worse and three expired.

Of the second series, an uncontrolled clinical trial of 84 patients, 44 were improved, 33 were unchanged and seven became worse. Changes within the individual symptom profile were most pronounced in the area of behavior, affective, withdrawn or aggressive; and in motor and psychomotor activity.

Side effects consisted primarily of extrapyramidal symptoms, which occurred in 10 patients in the first study, and 19 patients in the second.

The findings are suggestive, but not conclusive, of therapeutic activity by carphenazine in chronic schizophrenic patients. Symptomatic improvement occurred also in other diagnostic categories such as manic depressive psychosis, both manic and depressive types; mental deficiency with psychotic reaction; chronic brain syndrome—with senile brain disorder, chronic arteriosclerotic brain disease, or convulsive disorder; and psychoneurosis with anxiety reaction.

DISCUSSION

Dr. Douglas Goldman: Four of 50 chronic lowgrade schizophrenics with long hospital stay, showed much improvement. That is a good rate of improvement for such a group. I assume they would then have been transferred somewhere else.

Doctor McCreight: We could have released one male patient from the first series, and four from the second. The difficulty has been in the resistance of the families to taking them home.

Doctor Goldman: The point is that you could have reduced your population by 10 per cent. That is significant.

Doctor Page: An important factor in these studies is that there was wide variation in dosage. One wonders whether this could have influenced the results so as to make them appear within the realm of change.

Doctor Friedman: Were the patients in the first study as chronically ill as those in the second?

Doctor McCreight: Yes, they were. In both the controlled and the extended series we were dealing with the same type of chronically ill individual.

Factors That Determine Drug-Induced Akathisia

DANIEL X. FREEDMAN, M.D.* and JACOB DEJONG, M.D.†

A number of phenothiazine compounds produce symptoms ranging from restlessness and myoclonic twitches to dyskinesia, dystonia and parkinsonism.[1] "Restlessness" refers to a continuum of behavior; to objective movement patterns; and to impulsion to move the extremities, indeed to the effort required to inhibit the impulsion to such movement. This symptom complex has been termed "akathisia," the "inability to sit." The syndrome consists of motor restlessness and drivenness predominantly involving the extremities and often accompanied by subjective turmoil, which the patient frequently feels is different from his more familiar states of anxiety and discomfort. In fully developed form, akathisia can be recognized by the exaggerated, repetitive, stereotyped movements of the hands and feet and the response to anti-Parkinson treatment. Symptoms may develop after a few hours or days or several weeks of medication. The syndrome can develop under low dosage of phenothiazine agents fairly early in the course of treatment, and frequently independently of other parkinsonian symptoms. Concurrence of akathisia with other telltale manifestations of parkinsonism has been noted under high dosage of most phenothiazine compounds and with low doses of such phenothiazine derivatives as trifluoperazine.[2] Akathisia is generally relieved by administration of anti-Parkinson medication associated with the phenothiazine agent in use; or, on occasion, by simply shifting the dosage, or, almost invariably, by withdrawal of the offending drug.

With more extensive use of phenothiazine and Rauwolfia compounds, the syndrome is frequently encountered but often confused with an exacerbation of the target symptoms of agitation and hyperactivity. The level, duration and rate of increase of dosage are related to onset. Sarwer-Foner[3] has described a group of patients in whom dysphoric, dissociative or hyperactive reactions to tranquilizing agents developed on the basis of inability to tolerate drug-induced passivity and restraint or on a shift of the defensive structure. Akathisia can be distinguished from such psychogenic disturbances both by the characteristic symptomatic picture and by the prompt response to anti-Parkinson treatment.[4]

It is not clear whether the symptomatic picture is confined exclusively to disorders of the extrapyramidal system. The term "akathisia" was first used by Haskovec,[5] who, in 1904, observed the symptom in disorders he thought were of hysterical origin. In 1923 Bing[6] adopted the term to describe the symptom as it occurs in diseases of the basal ganglia. Freyhan, in the United States,[1] and Delay and co-workers,[7] in France, having in mind an extrapyramidal origin of the disturbance, applied the term "akathisia" to the drug-induced syndrome.

From the Psychopharmacology Laboratory, Departments of Psychiatry and Pharmacology, Yale University School of Medicine; Fairfield State Hospital, Newtown, Conn. This study is an extension and elaboration of an initial survey already reported.[9]

*Assistant Professor of Psychiatry; Career Investigator, N. I. M. H., Yale University School of Medicine, New Haven, Conn.

†Physician and Psychiatrist, Fairfield State Hospital, Newtown, Conn.

According to Wilson,[8] a similar symptomatic picture—"anxietas tibiarum"—was described in 1861 by Whitmaack, who referred to the peculiar imperative quality of painful conditions of unrest located in the deep tissues of the leg, which require movement as itching requires scratching. In the general medical literature of the past twenty years, a similar syndrome of unknown etiology has been frequently described as "restless legs."[10-12] These puzzling disorders are unrelated to tranquilizing drugs. Attempts have been made to explain them on a vascular or metabolic but rarely a psychogenic basis, and never to our knowledge have they been considered an expression of extrapyramidal dysfunction.[13]

In a broad sense, the occurrence of *drug-induced* extrapyramidal symptoms is referable to the central sites of pharmacologic activity of potent tranquilizing agents. Links between the action of the phenothiazine compounds and inter-related subcortical neural systems that subserve smooth and striate motor function, as well as interneural and behavioral alerting mechanisms have been established by neuropharmacologic research. These drugs act upon that complex of neural functions that bring us physiologically into contact with our internal and external milieu.[14,15]

The French authors, mindful that studies of the profound central neurovegetative effects of the phenothiazine derivatives preceded discovery of the tranquilizing and extrapyramidal effects, consider the whole range of these drugs as "neuroleptic" agents; i.e., nonhypnotic compounds with tranquilizing effects and pharmacologic activity on central sensorimotor substrates.[16] Apparently, such pharmacological alteration is a necessary (though perhaps not sufficient) condition for both tranquilizing and extrapyramidal effects. These effects are to an extent dissociable, since we frequently see tranquilization in the absence of extrapyramidal symptoms and the relative incidence of both effects may vary with different phenothiazine compounds. On clinical grounds, the frequency of parkinsonian symptoms has been considered an index of the relative tranquilizing potency of the various phenothiazine agents. Some clinicians[16] believe that the therapeutic efficacy of phenothiazine treatment is contingent not simply on an altered central substrate but also on the actual induction of extrapyramidal symptoms. Others[17] note the connection between such neural systems and the basic disease process *per se*. While such problems remain to be clarified, the occurrence of a perceptible symptom complex plays a considerable role in the evaluation of therapy with the phenothiazine compounds and theoretical speculation as to its basis.

Relatively few studies of the factors that contribute to development of drug-induced akathisia have been reported. It is probable that more is known than has been systematically presented. Delay and co-workers,[7] while believing that neuropharmacologic determinants are paramount, suggest that a hysterical element may be an important contributing factor in the development of overt symptoms. Freyhan[2] has explored sex as a determinant; he finds women prone to trifluoperazine-induced dystonia and men to akathisia, but such frequencies have not been generally established. Age and category of behavior pathology also have not been established as contributing factors; the disorder occurs in the young, in the senile and in normal volunteers.[3] The role of central neural pathology—e.g., posten-

cephalitic lesions—as a contributing factor has not been explored. In sum, neither personality nor individual somatic factors have been systematically investigated as variables in the incidence of drug-induced akathisia.

The critical determinants of the disorder are generally thought to be the basic structure of the phenothiazine molecule, the particular substitutions on the nucleus, and the dosage. The importance of these factors has emerged from clinical study.[18] Pharmacologic research, although it has established the central sites of activity of these agents, has not determined the presence of specific alterations in the neurochemistry of the central sensorimotor substrates related to akathisia. It has been observed that a piperazine or fluoro-substituent increases both akathisia and associated extrapyramidal symptoms.[19] The power of specific substituents to "lower" the threshold for akathisia is reflected in the fact that a low dose—fewer moles per gram of substrate—is sufficient to induce the syndrome. With each new manipulation of the basic structure, then, a change in the incidence of akathisia is to be expected.

We have sought to determine to what degree individual factors may contribute to the occurrence of akathisia. The study was designed to detect sensitive individuals; i.e., patients who might be expected to experience the disorder on *low* dosage and *early* (within 14 days) in the course of treatment. Since there is a point in the range of *high* dosages with phenothiazine agents at which we may expect a high incidence of extrapyramidal symptoms, including akathisia, we defined sensitivity as akathisia occurring within a short time and in the low range of dosages for the drugs tested.

We wished to discern (a) whether there are individuals with a low threshold for akathisia, and (b) whether there are polysensitive individuals (i.e., individuals sensitive to a number of substituents) or pansensitive persons (i.e., those sensitive to all agents containing the phenothiazine nucleus); (c) to assess the reliability with which a substituent produces the disorder, and (d) to determine whether the population as well as the variation in molecular substituents influences the incidence of akathisia.

Material and Methods

From the records of 800 chronically psychotic women, we selected 31 who were thought to have had akathisia. In the initial screening, the major selection factor was an order on the chart for anti-Parkinson drugs. There was no way to determine the rationale for such an order, but a "presumptively sensitive" group could be selected by these means. Phenothiazine agents and anti-Parkinson medication had been discontinued for all of these patients for at least six weeks prior to the study. Because reserpine may potentiate akathisia and show latent hematological and autonomic effects for months,[20] no patient was accepted if she had had reserpine within a year.

The mean age of the tested group was 55 years; the range, from 29 to 76. The average length of hospitalization was 11 years, with a range from 2½ to 27 years. The diagnoses covered the gamut of the schizophrenias.

Three compounds were initially investigated. Two had piperazine substitutions, and were known to induce akathisia in a significant percentage of individuals treated; i.e, prochlorperazine and perphenazine. The third agent, thioridazine, was selected because of its unique substituents and because it was

reported to produce few extrapyramidal effects.

The doses administered were half those usually prescribed in the hospital for schizophrenic patients; the dosage of the three compounds was equated for potency according to the local clinical concensus: prochlorperazine, 10 mg. twice a day; perphenazine, 4 mg. twice a day, and thioridazine, 50 mg. twice a day. The patients received medication in this dosage for eight days and then received twice the initial dose for the next four days, whereupon they received a placebo in the form of 800 mg. of meprobamate (Equanil®) twice a day four to seven days before the next sequence was instituted.

The total study had been preceded by a course of meprobamate, 800 mg. twice a day. Thus the effect of any interaction between meprobamate and the three compounds under study was assumed to be equal. The effect of possible interaction among the compounds tested could be detected by assigning the agents to the patients in a Latin square design.

This design was carried out for the initial study and produced a group that could be designated according to the sensitivities of the patients to the three tested drugs. This group was now available for testing other drugs.

A fourth agent, carphenazine, was tested on all subjects at the end of the rotations, in a dose of 15 mg. twice a day for eight days, and 30 mg. twice a day for another four days. All medications were administered in two Parke-Davis-00 pink capsules, twice a day.

The occurrence of akathisia was determined by physicians to whom the rotations were unknown and who evaluated the rating sheets filled in by the nurses and attendants, who also were blind to the content of the capsules and the intent of the study. Behavior was scored by a ward staff familiar with the patients' usual activity patterns and their variability over a number of years. For the purposes of this evaluation we accepted only unquestioned ratings of motor restlessness that occurred during the period of medication and disappeared during use of the active placebo (meprobamate). When akathisia was reported and scored, it generally was not reported after the third day of meprobamate medication; i.e., the scorable symptoms occurred with administration and disappeared on withdrawal of the treatment compound.

RESULTS

Sixteen of the 31 patients did not experience akathisia at all. The syndrome did develop in 15 patients (Table 1). These are referred to as groups A. B and C. The syndrome developed in four of the patients (group A) with perphenazine, prochlorperazine and thioridazine. When the disorders were assessed according to intensity, these four patients experienced the most severe and extensive restlessness, complaints, and various associated parkinsonian symptoms. Akathisia developed in only four patients (group B) during medication with perphenazine and prochlorperazine, but not thioridazine. Akathisia developed in seven patients (group C) on only one of the three tested drugs. It is clear that this sample can be grouped along a continuum of sensitivity from the most of the least sensitive individuals.

In a repeat study of all these patients, the individuals retained their group membership; such patients would provide a highly consistent group for further study. In both trials, the onset of symptoms varied from the second to the eleventh day, so that we cannot characterize the patients or the drugs on this

TABLE 1

Akathisia Induced by Phenothiazine Compounds

Group*	Patient No.	COMPOUNDS ADMINISTERED							
		Perphenazine		Prochlorperazine		Thioridazine		Carphenazine	
		Test 1	Test 2	Test 1	Test 2	Test 1	Test 2	Test 1	Test 2
A	1	X	X	X	X	X	X	X	X
	2	X	X	X	X	X	X	X	X
	3	X	X	X	X	X	X	X	X
	4	X	X	X	X	X	X	O	O
Percentage Akathisia Induced 94%									
B	5	X	X	X	X	O	O	X	X
	6	X	X	X	X	O	O	X	X
	7	X	X	X	X	O	O	O	O
	8	X	X	X	X	O	O	O	O
Percentage Akathisia Induced 63%									
C	9	X	X	O	O	O	O	X	X
	10	X	X	O	O	O	O	O	O
	11	X	X	O	O	O	O	O	O
	12	X	X	O	O	O	O	O	O
	13	O	O	X	X	O	O	O	O
	14	O	O	X	X	O	O	O	O
	15	O	O	O	O	X	X	O	O
Percentage Akathisia Induced 29%									
D	16	O	O	O	O	O	O	X	X
		Akathisia did not develop in patients 17-31							
Total incidence %**		75		63		31		44	

*These groupings were originally classified on the basis of a test in the initial study.[9]
**Differences in the amount and duration of the dosage could alter the incidence of akathisia induced by each agent.

basis. The length of time over which the sensitivity groupings persisted was not tested beyond the seven month period of this report. It is possible that fluctuations in the condition or the metabolism of the patient might change the picture on subsequent trials with the identical drugs.

After completion of this study and the investigation of carphenazine, we found that many "nonreactors" did react specifically to the compound they were taking (perphenazine, mepazine, chlorpromazine, reserpine) at the time anti-Parkinson medication was begun, but invariably the dosage necessary to induce akathisia was in the high clinical range. The specificity of low dose akathisia was further demonstrated by repeatedly testing selected individuals; e.g., the patient from group C in whom akathisia developed during testing with thioridazine (the drug with the lowest over-all incidence of the reaction in this study) did so on repeated trials. For each individual in group A we eventually found a potent phenothiazine derivative that did not induce akathisia.

When we tested a fourth phenothiazine compound, carphenazine, we found that the groups retained their rank order, but individuals within the groups did not; i.e., the percentage of reactions was greater in group A than in groups B or C. Akathisia developed in one of the 16 "nonreactors" (Group D) treated

with this compound. In a repeat trial, the results were reproduced. Only a small percentage of patients were affected by carphenazine, but the reactions that did occur were notably prompt in onset and intense (stereotyped movements). It is clear that intensity and frequency of akathisia must be differentiated.

DISCUSSION

The results indicate that there are individuals who have a low threshold for akathisia. These patients are not indifferent to the substituent on the phenothiazine nucleus but rather show specific sensitivity to specific configurations; i.e., there are polysensitive but *not* pansensitive persons.

Among individuals with a low threshold, we can define a continuum of sensitivity based on the number of substituents to which an individual shows a specific response. Particular substituents (e.g., piperazine) appear to be specific for a larger number of individuals than other molecular moieties; in a *small* group of patients a large number of different molecular structures induce akathisia. Hence, the incidence of low dose akathisia would depend on the population tested as well as on the compound used.

This study was not intended to compare the relative akathisia-inducing potencies of various substituents administered at the usual clinical dose levels. It *is* possible that the specific substituents would show a different incidence with different dosage schedules, although the order of akathisia-inducing potency of substituents in these experiments is in accord with clinical studies.[2]

When we tested the nonreactors with the drug with which they had earned (justly or not) anti-Parkinson medication, some became reactors when the dosage was high and sustained. We concur with the opinion that dose and period of treatment are critical factors in the incidence of akathisia. In our study the disorder developed at different times within the test period of two weeks in individuals on repeat trials. Duration of dosage within that period was not a differentiating factor. Time of onset did not seem to be a property of the substituent groups except in the studies with carphenazine. The various studies of this agent in humans and animals seem to coincide in terms of time factors. Intensity of response seemed to be determined by population and by the substituents. In the polysensitive group A, any instance of akathisia was more severe than in the other groups, yet in one of these patients akathisia did not develop in repeated trials when the capsule contained carphenazine. When carphenazine did induce akathisia among the reactors of any group, the reaction was always prompt and intense.

Among the four groups tested, we could not discern any differentiating psychomotor, temperamental, psychosocial or diagnostic features; elucidation of such factors awaits an experiment designed to test for them. We have the impression that the facility with which a patient perceives and communicates the presence of akathisia may be dependent on personality factors. Not every patient presses his complaints, and in tours of large wards we have detected the disorder by objective signs and have been able to elicit complaint only by deliberate inquiry. Once a patient has experienced akathisia and relief from it, he characteristically will seek relief from the next episode. Whether perception of akathisia and purposeful response to it contribute to the intensity of the reaction is a moot point. These factors do not bear on the

major results of this study since all the patients had had akathisia and relief from it; we relied on objective scores and found that each patient reacted specifically to the presence and absence of specific substituents in the capsules.

The fact that an extrapyramidal symptom shows chemical specificity is not necessarily surprising. Biological specificity for molecular structure has been demonstrated in a number of pharmacologic studies. In view of the relationship between extrapyramidal symptoms and tranquilization, the question arises as to whether phenothiazine compounds have the same specificity for tranquilizing potency in the individual as they do for side effects. The psychosocial influences on drug effect and psychosocial and methodologic variables that influence *evaluation* of a drug in clinical practice are well appreciated. The operation of such factors may account for an impression that there is relatively little therapeutic difference among various groups of phenothiazine derivatives. The confusing proliferation of compounds and claims thus has led to an understandable perplexity. These findings remind us of the possibility that individuals differ in their "molecular requirements" for response. Currently, numerous drugs are tested on large numbers of patients, and the superiority of one compound over another for an individual is difficult to assess. Further chemical developments and the skilful application of evaluative procedures in individual case study as well as in group study may yet disclose a biological specificity for the desired effects as well as for the side effects of tranquilizing agents. The threshold for development of akathisia seems to depend on individual sensitivity to the molecular configuration, and the quantity, duration and rate of increase of dosage of the agent used.

These findings have practical significance: (1) Screening groups for testing molecular moieties are available. (2) Once akathisia develops it should *not* be assumed that the patient belongs to a polysensitive group (e.g., group A) and will show a low threshold for any phenothiazine compound. (3) A phenothiazine derivative may exist to which a polysensitive subject will show no sensitivity. (4) It seems likely that any potent tranquilizer has a neuroleptic action and will induce akathisia in some individuals. (5) An agent that induces an intense akathisia need not induce a high frequency of such reactions. (6) Certain compounds may induce a high frequency of reactions but not necessarily the most intense reactions. (7) Population has a distinct bearing on the incidence of akathisia (Table 1).

SUMMARY

The factors that determine the incidence of drug-induced akathisia were studied in 31 psychotic women who received four different phenothiazine compounds. The findings indicate that low dose akathisia results from an individual specific sensitivity to a specific molecular configuration. There is a population with a low threshold for the disorder. Thresholds are determined by the spectrum of individual sensitivities for specific molecular configurations, and the dose level, period and rate of increase of dosage with such configurations. The incidence and intensity of *low dose* akathisia are to a degree independent and are influenced by at least two factors: the population tested and the specific molecular structure of the agent used.

The foregoing study was supported by Grant M-1204 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

The drugs used in this study were supplied by Wyeth Laboratories, Sandoz Pharmaceuticals, Schering Corporation, and Smith Kline & French Laboratories.

Acknowledgment: We are grateful for the advice of Dr. Jane Oltman and the aid of the nursing and attendant staff of the Fairfield State Hospital.

REFERENCES

1. Freyhan, F. A.: Psychomotility and Parkinsonism in Treatment with Neuroleptic Drugs. *Arch. Neurol. & Psychiat.,* 78:465-472, 1957.
2. Freyhan, F. A.: Occurrence and Management of Extrapyramidal Syndromes in Psychiatric Treatment with Trifluoperazine, in Brill, H.: "Trifluoperazine, Clinical and Pharmacological Aspects," Philadelphia, *Lea & Febiger,* 1958.
3. Sarwer-Foner, G. J., editor: "The Dynamics of Psychiatric Drug Therapy," Springfield, Ill., *Charles C Thomas,* 1960.
4. Sarwer-Foner, G. J.: Recognition and Management of Drug-Induced Extrapyramidal Reactions and "Paradoxical" Behavioral Reactions in Psychiatry. *Canad. M. A. J.,* 83:312-318, 1960.
5. Haskovec, L.: Weitere bemerkungen ueber die akathisie. *Wien. med. Wchnschr.,* 54: 526-530, 582-586, 1904.
6. Bing, R: Ueber einige bemerkenswerte begleiterscheinungen der "extrapyramidalen rigidität" (akathisie-mikrographie-kinesia paradoxa). *Schweiz. med. Wchnschr.,* 4: 167-171, 1923.
7. Delay, J., Deniker, P., Green, A., and Mordret, M.: Le syndrome excitomoteur provoqué par les medicaments neuroleptiques. *Presse méd.,* 65:1771-1774, 1957.
8. Wilson, S. A. K.: "Neurology," Baltimore, Md. *Williams & Wilkins,* 1940.
9. Freedman, D. X., and de Jong, J.: Thresholds for Drug-Induced Akathisia. *Am. J. Psychiat.* (in press).
10. Ekbom, K. A.: Restless Legs. *Acta med. scandinav., Supp.,* 246:64-68, 1950.
11. Ekbom, K. A.: Restless Legs Syndrome. *Neurology,* 10:868-973, 1960.
12. McGavack, T. H., Elias, H., and Boyd, L. J.: Some Pharmacological and Clinical Experiences with Dimethyaminoethyl Benzhydryl Ether Hydrochloride (Benadryl). *Am. J. M. Sc.,* 213:418-434, 1947.
13. Masland, R. L.: Myokymia—a Cause of "Restless Legs." *J.A.M.A.,* 134:1298, 1947.
14. Freedman, D. X., and Giarman, N. J.: Apomorphine Test for Tranquilizing Drugs: Effect of Dibenamine. *Science,* 124: 264-265, 1956.
15. Himwich, H. E.: Psychopharmacologic Drugs. *Science,* 127:59-72, 1958.
16. Deniker, P.: Psychophysiologic Aspects of the New Chemotherapeutic Drugs in Psychiatry. *J. Nerv. & Ment. Dis.,* 124:371-376, 1956.
17. Ostow, M.: Effects of the Newer Neuroleptic and Stimulating Drugs on Psychic Function, in "The Dynamics of Psychiatric Drug Therapy," edited by G. J. Sarwer-Foner, Springfield, Ill., *Charles C Thomas,* 1960.
18. Goldman, D.: Personal communication.
19. Kinross-Wright, J.: Newer Phenothiazine Drugs in Treatment of Nervous Disorders. *J.A.M.A.,* 170:1283-1288, 1959.
20. Freedman, D. X., and Benton, A.: "Persisting Effects of Reserpine in Man." *New England J. Med.* (in press).

Comparison of the Clinical Effects of Carphenazine and Fluphenazine in Chronic Schizophrenics

ANTHONY SAINZ, M.D.*

For a long time the efforts of the Division of Research at Marcy State Hospital have been directed toward combating the disabling effects of schizophrenia in the chronic form. Evaluation in 1956 of studies performed with mepazine during 1955 showed that this drug was able to effect partial or total remission in a significantly higher proportion of chronic schizophrenics than did chlorpromazine (9 per cent versus 3 per cent). This suggested the importance of phenyl derivatives as prosthetic radicals in the phenothiazine molecule. Similar results were obtained in the following year with intramuscular administration of phenyltoloxamine, which, although a diphenyl derivative, has a structure resembling a pyrimidine ring, such as is found in mepazine. Oral administration of phenyltoloxamine was ineffective, probably because the simple structure of the molecule lent itself to rapid deamination in the liver. Fluphenazine was evaluated in this institution in 1958, after it had been found the most active of several similar compounds. This drug proved twice as effective as mepazine or phenyltoloxamine in chronic schizophrenics, particularly of the hypodynamic subtype. Fluphenazine had the additional curious property of being totally ineffective in early schizophrenia (i.e., duration of symptoms for less than two years).

Early in 1959 we began the evaluation of carphenazine. In addition to the study in human pharmacology (see page 28), evaluation by the Marcy Psychiatric Rating Scale was carried out in schizophrenics of the recent and chronic subtypes as defined in "Rapid Screening of Phrenopraxic Drugs." The series comprised 163 patients (92 females, 71 males), ranging in age from 14 to 68 years. Of this number 26 belonged to the recent subtype; and 137 to the chronic subtype (i.e., they had suffered psychotic episodes for at least three years or longer, or had been continuously ill without remission). Fifty-three per cent were of the paranoid variety; 42 per cent were of the catatonic, and 5 per cent were of the hebephrenic, or simple, schizophrenic subgroups. Thirty-three patients were removed from the group because they were placebo reactors and were totally uncooperative toward oral medication, withdrawal of medication, or revision of diagnosis. One hundred and thirty patients actually received medication for a minimum of six months, according to the triple blind controlled procedure described in "On a Methodology for the Clinical Evaluation of Phrenopraxic Drugs."[1]

Patients receiving mepazine and fluphenazine were used as controls. Three hundred chronic schizophrenic patients were treated with mepazine, and 219 received fluphenazine.

The therapeutic results are expressed in percentages based on a weighted calculation for the purpose of comparing the effects of carphenazine treatment with those obtained in the comparable groups treated with mepazine and fluphenazine, following strictly identical

From the Marcy State Hospital, Marcy, N.Y.
*Director of Research, Marcy State Hospital, Marcy, N. Y.

research designs and methodological procedures. The level of confidence is 0.85 for the three groups compared, which thus makes this a statistically valid study.

To obtain the highest validity, only ranks 1 and 2 of the Marcy Psychiatric Rating Scale were taken into consideration as indicative of a satisfactory therapeutic result. From the over-all view, these ranks were achieved in the chronic subtype by 9 per cent of those treated with mepazine, 18 per cent of those treated with fluphenazine, and 34 per cent of those treated with carphenazine. These ranks were also reached in the recent subtypes by 57 per cent under mepazine treatment, 40 per cent under carphenazine treatment and 0 per cent with fluphenazine medication.

These figures clearly show that carphenazine is much more effective than fluphenazine in schizophrenias of the chronic subtype. Detailed study of the clinical evaluation of the chronic patients treated with carphenazine also shows that this subtype should be divided into two groups: the hypodynamic, characterized by maximum autism and anergia; and the hyperdynamic, characterized by overactivity, hallucinations and agitation. In the hypodynamic category 38 of the 95 patients reached the target ranks, while only two of 35 patients in the hyperdynamic group achieved equal improvement. This undoubtedly shows the high specificity of carphenazine, and probably the high specificity of the disorder also.

The compound was administered orally in all cases and urinary excretion of the substance was verified at random in every patient. The starting dose was 25 mg. four times daily; this was doubled every week or two. The largest dose was 500 mg. administered four times daily for two weeks. The maximum therapeutically useful dose was found to be 300 mg. orally, four times daily. The minimum effective dose was 25 mg. orally, four times daily.

Side effects were remarkably few with this medication; no toxic complications were observed. The commonest side reaction was drowsiness, which affected 10 per cent, or 13 of the study group. Dryness of the mouth occurred in 5 per cent; extrapyramidal reactions, in 2 per cent; and postural hypotension, in 1 per cent. No skin rashes, allergic manifestations or constipation developed.

All the side effects tended to disappear spontaneously and required no treatment. Persistent drowsiness temporarily required small amounts of amphetamines on arising in some cases, and caffeine or an anticholinergic was sometimes necessary to control extrapyramidal reactivity. Emergence of a side effect or an intercurrent infection was not considered an indication for reduction of dosage or discontinuation of treatment.

An interesting observation was that patients who were in contact with others receiving fluphenazine, or who had taken fluphenazine themselves before carphenazine was started, showed a high incidence of pseudoparkinsonian reactions, notably imitation of akathisia and rigidity. This was soon discovered because most showed their pseudoparkinsonian reactions during placebo medication or soon after the start of carphenazine treatment and the symptoms invariably subsided on injection of sterile water. Numerous other reactions were feigned by the placebo reactors, or "mimic schizophrenics" (a name we have given to the patients sufficiently in contact and sufficiently negativistic to resist medication and to imitate actual

side effects they see or hear of, thus to bolster their avoidance of treatment or prove they were being "made worse"). Some of the placebo reactors feigned seizures, oculogyric crises, vertigo and shaking spells.

Our studies led us to the impression that carphenazine is the drug of choice for chronic, hypodynamic schizophrenics, and may even be the treatment of choice for the chronic schizophrenias.

DISCUSSION

Dr. Heath: I am curious as to the use of the terms "hyperdynamic" and "hypodynamic." What were the pseudoparkinsonian symptoms described?

Dr. Sainz: We want to imply that there is an excess of psychic activity, and not necessarily motor overactivity alone. Mainly, there is an increase in dereistic thinking, and increase in hallucinatory experiences and illusional patterns.

The patients, in presenting pseudoparkinsonian reactions, tended to imitate, first, the gait of the akathisic patient, and the shaking leg movements. They tried to imitate those they had been in contact with, or they tried to imitate reactions they had had in the past. They all seemed to develop a different gait. Some shuffled, some stepped up and down, and others walked stiffly, according to their own interpretation. Differentiation of the feigned from the actual Parkinson symptoms was frequently difficult.

REFERENCE

1. Sainz, A., et al.: On a Methodology for the Clinical Evaluation of Phrenopraxic Drugs. *Psychiat. Quart.*, 31:10-16, 1957.

Summary of the Findings in Pharmacological and Clinical Studies of Carphenazine

JOSEPH M. TOBIN, M.D.*

In recapitulating the data presented at this symposium an attempt will be made to determine whether the basic hypotheses referred to in the introduction have been supported: that is, whether it is possible, in a basic piperazinyl compound with known antipsychotic activity, to substitute a propionyl group at the second position on the phenothiazine ring so as to widen the gap between the optimum therapeutic dose and the dose that produces extrapyramidal symptoms without at the same time altering the essential ataractic action of the compound. Investigation of carphenazine was begun in the belief that troublesome pharmacologic by-effects or toxic side actions are not necessarily a corollary to optimum therapeutic activity. This concept has been accepted in the practice of medicine for centuries.

Pharmacological studies have shown that the compound possesses peripheral, antiadrenergic and anticholinergic properties, as demonstrated by (a) protection of mice, rabbits and cats against lethal doses of amphetamine and against morphine excitement; and (b) blocking of the effects of Tremorine in mice. Acute and chronic toxicity experiments indicated that carphenazine, in therapeutic dosage, produces no potential hazard to body systems. The electrophysiologic changes, consisting of increased voltage, reduced frequency and high synchrony (Hosko) appeared to be consistent in both animal and human subjects. These experiments would further indicate that there is definite blocking effect in the ascending reticular activating system, as shown by antagonism to amphetamine stimulation.

On the clinical level a mild, transient hypotensive response (10 to 20 mm. Hg systolic and 10 to 15 mm. Hg diastolic) has been suggested, but has not been borne out by any significant statistical evidence, and does not appear to constitute a problem in administration of the compound. Changes in respiratory and kidney function and in blood morphology have not been observed. Cacioppo and co-workers reported two cases of increased cephalin flocculation values in their study. This compares with four cases in the trifluoperazine group.

The clinical effectiveness of carphenazine was studied in 727 patients in the investigations reported in this symposium. Six hundred eighty-seven were afflicted with chronic schizophrenia; the remainder exhibited a wide variety of psychotic reactions associated with functional mental disorders or organic brain disease. The patients ranged in age from 11 to 83 years. The chronicity of symptoms followed the usual pattern seen in mental institutions. A digest of the seven clinical series is presented in Table 1. In an additional study, Freedman and DeJong explored the extrapyramidal reactivity of the compound in 31 specially selected, sensitized patients.

The total patient population cannot be regarded as homogeneous, even within broad diagnostic categories. The greatest emphasis was laid on treatment of schizophrenia, the complexities

*Director, Bureau of Research in Neurology and Psychiatry, New Jersey Neuropsychiatric Institute, Princeton, N. J.

TABLE 1

Digest of Seven Clinical Studies of Carphenazine

	Oltman & Friedman*	Cacioppo et al.*	Merlis†	Goldman†	Kothari et al.†	McCreight*†	Sainz*	Over-all totals
Total carphenazine-treated patients, each study	123	52	15	228	48	47* 84†	130	727
Diagnoses								
Schizophrenic in-patients	123	51		228	48	47* 50†	130 (95 hypodynamic) (35 hyperdynamic)	677
Schizophrenic out-patients			10					10
Manic-depressive psychosis						9†		9
Psychoneurosis			4			3†		7
Involutional psychosis, paranoid						1†		1
Character disorder			1					1
Alcoholism						1†		1
Chronic brain syndrome						11†		11
Mental deficiency		1				9†		10
Sex—Males	0	52	4		48	23* 12†	44%	139 recorded
Females	123		11			24* 72†	56%	230 recorded
Age—Range, yrs.	14–62	21–59	11–56			24–68* 19–83†	14–68	
Median or average, yrs.						—* 42†		
Duration of Hospitalization								
Range (All patients chronically ill)	A few days (this episode) to 31 yrs.	3-33 yrs.	1-18 yrs.	prolonged	2-21 yrs.	2-38 yrs.* 3 mos. to 46 yrs.†	Psychotic episodes or continuously ill for 3 yrs. or more	A few days to 46 yrs.
Median or average	<1 yr. 48% 1-2 yrs. 21% >2 yrs. 31% 16 pts.—19 yrs.				10 yrs.	7-8 yrs.†		<1 yr. to 19 yrs.
Duration each treatment period, or duration of total treatment	4-8 wks each treatment period, carphenazine and active placebo	9 wks.	Up to 7 mos.	1 to 6 mos. or more	2-8 mos.	About 7 mos.	Minimum of 6 mos.	Overall average duration between 5 & 6 mos.

*Controlled—†Uncontrolled

of which were ably described in the paper by Nolan D. C. Lewis, and in the discussion of Dr. Lewis's paper by Nathan Kline. It was not possible to ascertain the precise degree of severity of the schizophrenic process—the state of regression toward apparent deterioration—present in each patient under observation. However, by using the duration of hospitalization as an index of chronicity, it will be seen that a preponderance of the cases fell in the classification of established schizophrenia.

Prior to the introduction of psychotherapeutic agents, the incidence of spontaneous improvement to any degree among chronic schizophrenics hospitalized more than two years and less than five years was somewhere in the neighborhood of 15 to 20 per cent. For patients hospitalized three to five years, about 5 per cent might have been expected to improve to some extent, and after five years the expectation of a measure of remission fell to as low as 1 per cent. No reliable statistics based on duration of hospitalization, by which the prospect of even partial remission may be predicted, have been compiled since the advent of psychopharmacologic compounds. Experience indicates, however, that improvement may occur in not much more than about 30 per cent of those hospitalized two to five years, and in no more than 10 per cent of those hospitalized over five years.

Carphenazine is a particularly interesting compound because its therapeutic action in schizophrenia seems not to be specifically related to the chronicity of the illness, according to the data accumulated in these studies. Improvement was graded as *pronounced* (rated A) in about 20 per cent; *moderate* (rated B) in about 35 per cent, thus 55 per cent showed some degree of improvement. A rating of *slight* improvement to *no change* (C to D) was assigned to about 43 per cent. About 2 per cent became *worse* or more agitated (E) under the medication. Two patients died during the study from causes unrelated to carphenazine treatment.

Interpretation of the results is not easy and in some instances the figures themselves may fail to demonstrate the true basic effectiveness of the compound. There are definite indications that the most favorable response occurs in the presence of regression, withdrawal, seclusiveness, mutism, apathy, bizarre posturing, blocking of speech and of logical thinking, and delusions or hallucinations or both. On the other hand, patients who exhibit a high degree of motor hyperactivity and agitation may well deteriorate further under the medication.

The influence of age of the patient on the response to carphenazine is of some interest. Some degree of improvement was observed in 90 per cent of those less than 20 years old; in 66 per cent of the 20 to 30 year age group; in 65 per cent of those 30 to 40; in 54 per cent of patients 40 to 50; and in 41 per cent of those more than 50 years old. This represents a surprisingly large percentage of symptomatic improvement in the older age group.

A favorable response was slightly more frequent among the females (56 per cent) than among the males (50 per cent).

Oltman and Friedman noted a relationship between the response and the nature of onset of the symptoms. They obtained remission in 78 per cent of those who had experienced an acute onset, but in those who had had an insidious onset the percentage of improvement was significantly smaller.

Goldman's studies showed that evidence of optimum therapeutic effect is

not to be expected, in a chronic schizophrenic population, in less than three months of treatment. His data on a single group, treated first for one to three months and then for three to six months or longer, show a progressive shift toward improvement as medication continued. This information is of considerable importance in assessment of the real significance of the results obtained in blind studies, when an agent has been administered for limited periods only; e.g., less than three months (Oltman and Friedman, Cacioppo and co-workers). It is essential to realize that relatively nonspecific phenothiazine compounds cannot be expected to produce clearly recognizable changes in a long established illness, such as chronic schizophrenia, in a short period of treatment. Table 1 shows the duration of medication in each of the series reported.

Optimum therapeutic dosage is probably the most difficult feature to determine from the data presented. Individualization is imperative. In measuring the dosage on the basis of an arbitrary subdivision of the patients, according to the total duration of the illness, before starting medication, it became apparent that for patients who have been ill for more than three years and show signs of regression, the initial dose should be 50 mg. three times daily. It is important to increase the dose gradually, at weekly intervals, in amounts of not more than 25 to 50 mg. per day, until an optimum therapeutic response is obtained or side reactions supervene.

In the studies of Cacioppo and coworkers on chronically ill schizophrenic in-patients, the optimum therapeutic effects with carphenazine were noted in the 75-100 mg. dose range and were not associated with parkinsonian reactions.

When the symptoms are more labile, it appears the patients respond more favorably, in most instances, to carphenazine in initial doses of 25 mg. three times a day. To obtain a more rapid therapeutic effect in this group the daily dose may be increased by increments of 25 mg. until the desired response, or somnolence or mild akathisia, develop. For the chronic schizophrenic undergoing hospitalization for an acute exacerbation, the same type of dosage regimen may be applied. In the ambulatory chronic schizophrenic initial oral doses of as low as 12.5 mg. three times daily would appear to be adequate; this dose may be gradually increased by daily increments of 12.5 mg., as required. Acute schizophrenic reactions should be treated with initial oral doses of 12.5 to 25 mg. three times a day, which may be increased rapidly, as indicated by the clinical response, to a maximum of 100 mg. daily.

These recommendations should not be regarded as rigid criteria for administration, particularly since individual sensitivity to phenothiazine compounds seldom can be predicted. Therefore for initial treatment, most of the dosages prescribed should lie in the lower range. Experience indicates that optimum therapeutic effects with low incidence of extrapyramidal symptoms may be obtained by gradual increase of the dose at seven to fourteen day intervals.

Somnolence, a common side effect, can be used as an indicator for adjustment or stabilization of dosage. The characteristic drowsiness, combined with the relatively short activity of the individual dose, as reported by both Tislow and Stein, gives flexibility to medication with the compound.

Table 2 indicates the incidence of side effects in each series. The side actions that occurred may be classified as: (a) *extrapyramidal* (parkinsonian

TABLE 2
Side Effects of Carphenazine

	Oltman & Friedman 123 pts.	Cacioppo et al. 52 pts.	Merlis 15 pts.	Goldman 228 pts.*	Kothari et al. 48 pts.†	McCreight 47 & 84 pts.	Sainz 130 pts.‡
Parkinsonian syndrome	22	5	1	oral 32	0	12	6
				I.M. 5		1	
Akathisia	9			11		1	
Oculogyric crises	1						
Rigidity					5		
Tremor					1	2	
Muscle pain					1		
"Mainly extrapyramidal," or bizarre posturing with extrapyramidal symptoms						19 (of 84 pts.)	1
Dystonia				oral 7			
				I.M. 2			
Lethargy		5					
Somnolence			1	oral 37			13 (10%)
				I.M. 11			
Turbulence				8			
Agitation		1				5	
Alteration in cephalin flocculation values		2					
Mild postural hypotension				1	1		8
Dizziness						2	
Salivation						1	
Mouth dryness							5%
Sweating						1	

*15 pts. with parkinsonism and 1 with akathisia required Artane.
†Sedation and extrapyramidal reaction mild and infrequent.
‡All side effects tended to disappear without treatment.

syndrome, akathisia, dystonia, oculogyric crises) and (b) *peripheral* (such as somnolence, lethargy, nausea, salivation, sweating, dizziness and, in rare instances, mild postural hypotension).

In the largest series of the investigation, that of Goldman, fully developed extrapyramidal disturbances occurred in 19 per cent, a higher incidence than that seen in the series reported by Sainz, although the over-all chronicity of the cases in Sainz's study was probably greater. Oltman and Friedman reported an incidence of 18 per cent extrapyramidal symptoms in a series of chronic patients treated during acute exacerbation of the schizophrenic process.

Extrapyramidal side reactions appear to be readily controlled by administration of anti-Parkinson agents, intravenously for relief of oculogyric crises, or orally for treatment of other extrapyramidal manifestations.

From all these data it would appear that the original hypotheses are supported: that carphenazine is an active antipsychotic agent, and that medication with this compound is associated with flexibility of dosage and low toxicity and with a relatively low incidence of extrapyramidal reactivity.